DOCUMENT RESUME

ED 047 452 EC 031 594

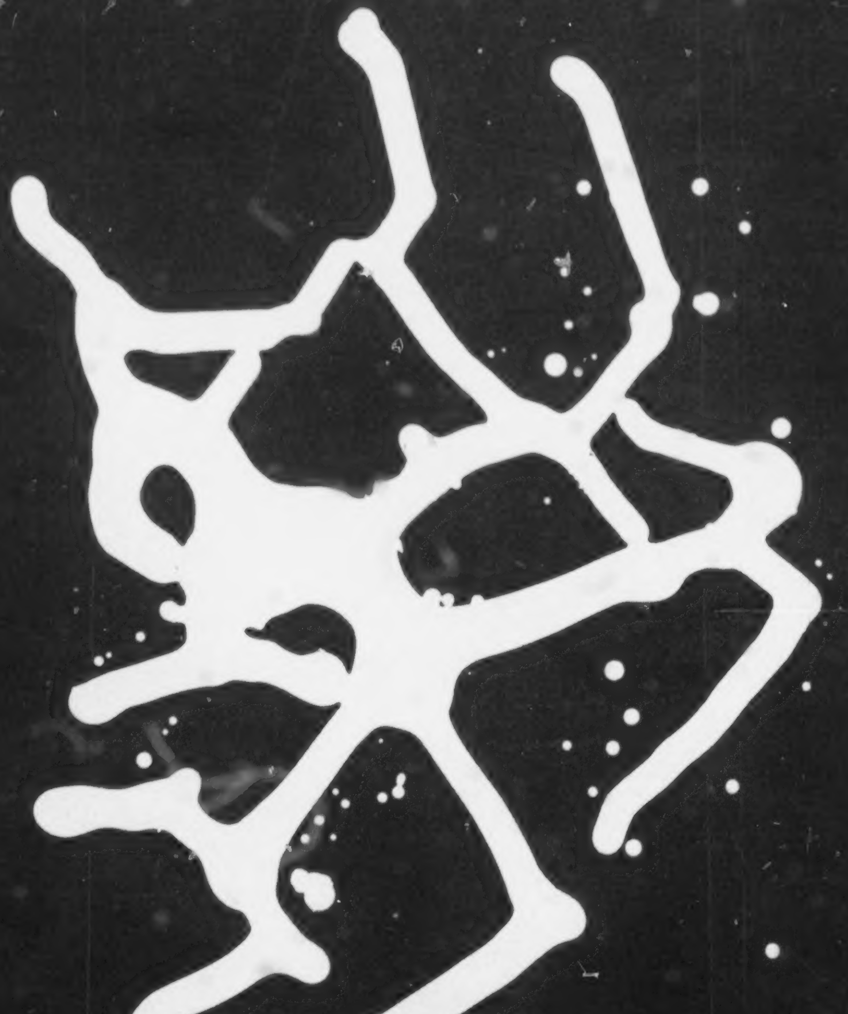
AUTHOR	Angle, Carol R., Ed.; Bering, Edgar A., Jr., Ed.
TITLE	Physical Trauma as an Etiological Agent in Mental Retardation.
INSTITUTION	National Inst. of Neurological Diseases and Stroke (DHEW), Bethesda, Md.; Nebraska Univ., Lincoln. Coll. of Medicine.
PUB DATE	70
NOTE	311p.; Proceedings of a Conference on the Etiology of Mental Retardation (Omaha, Nebraska, October 13-16, 1968)
AVAILABLE FROM	Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 ($3.75)
EDRS PRICE	EDRS Price MF-$0.65 HC Not Available from EDRS.
DESCRIPTORS	Conference Reports, Etiology, *Exceptional Child Research, Incidence, *Infancy, *Injuries, *Medical Research, *Mental Retardation, Neurological Organization, Neurology, Pathology, Premature Infants, Prenatal Influences
IDENTIFIERS	Pediatrics

ABSTRACT

The conference on Physical Trauma as a Cause of Mental Retardation dealt with two major areas of etiological concern - postnatal and perinatal trauma. Following two introductory statements on the problem of and issues related to mental retardation (MR) after early trauma to the brain, five papers on the epidemiology of head trauma cover pathological aspects, terminal hemorrhages in the brain wall of neonates, postmortem neuropathologic findings in birth-injured patients, and epidemiological studies. Nine papers report perinatal studies on such topics as obstetric history, obstetric trauma, fetal head position, maternal pelvic size, birth position, intrapartum uterine contractions, and related fetal head compression and heart rate changes. Five special studies of the developing brain concern trauma during labor, trauma to neck vessels, the immature brain's reaction to injury, partial brain removal in infant rats, and cerebral ablation in infant monkeys. The following aspects of the premature infant are discussed in relation to MR in five papers: intracranial hemorrhage, CNS damage, clinical evaluation, EEG and subsequent development, and hematologic factors. Five papers on postnatal trauma examine subdural hematoma and its etiology, the battered child, an interdisciplinary prospective study, and intellectual sequelae of coma due to acceleration concussion. (KW)

FEB 18 1971

ED0 47452



304

PHYSICAL TRAUMA
AS AN ETIOLOGICAL AGENT IN MENTAL RETARDATION

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
National Institutes of Health Public Health Service

EC031594

PHYSICAL TRAUMA AS AN ETIOLOGICAL AGENT IN MENTAL RETARDATION

Proceedings of a Conference on the Etiology of Mental Retardation,
October 13–16, 1968, Omaha, Nebraska

ED0 47452

Carol R. Angle, M.D.
Department of Pediatrics
University of Nebraska
College of Medicine
Omaha, Nebraska

Edgar A. Bering, Jr., M.D.
National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

U.S. Department of Health, Education, and Welfare
Public Health Service
National Institute of Health
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland 20014
1970

U.S. DEPARTMENT OF HEALTH, EDUCATION & WELFARE
OFFICE OF EDUCATION

THIS DOCUMENT HAS BEEN REPRODUCED EXACTLY AS RECEIVED FROM THE PERSON OR ORGANIZATION ORIGINATING IT. POINTS OF VIEW OR OPINIONS STATED DO NOT NECESSARILY REPRESENT OFFICIAL OFFICE OF EDUCATION POSITION OR POLICY.

This conference was sponsored by
The National Institute of Neurological Diseases and Stroke
Bethesda, Maryland
and
The College of Medicine
University of Nebraska
Lincoln, Nebraska

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402—Price $3.75

PROGRAM PLANNING COMMITTEE

Carol R. Angle, M.D., *Chairman*
Ellsworth C. Alvord, Jr., M.D.
Edgar A. Bering, Jr., M.D.
Loring Chapman, Ph.D.
John A. Churchill, M.D.
Sherwood A. Jacobson, M.D.

8 4

PARTICIPANTS

Raymond D. Adams, M.D., *Chairman*
Chief, Neurology Service
Massachusetts General Hospital
Boston, Massachusetts

Ellsworth C. Alvord, Jr., M.D.
Professor of Pathology
University of Washington
School of Medicine
Seattle, Washington

George W. Anderson, M.D.
Associate Professor of
Obstetrics & Gynecology
Tufts University School of Medicine
Boston, Massachusetts

Carol R. Angle, M.D.
Associate Professor of Pediatrics
University of Nebraska College
of Medicine
Omaha, Nebraska

James S. Apthorp, M.D.
Assistant Professor of Pediatrics
University of Southern California
School of Medicine
Los Angeles, California

Charles F. Barlow, M.D.
Bronson Crothers Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Heinz W. Berendes, M.D.
Chief, Perinatal Research Branch
National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

Edgar A. Bering, Jr., M.D.
Special Assistant to the Director for Program
Analysis, National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

Perry Black, M.D., C.M.
Assistant Professor of Neurological
Surgery and Psychiatry
Johns Hopkins University School of Medicine
Baltimore, Maryland

Roberto Caldeyro-Barcia, M.D.
Professor and Chairman, Department
of Physiopathology
Hospital De Clinicas
Montevideo, Uruguay

Coldevin B. Carlson, M.D.
Assistant Professor of Medicine and Pediatrics
University of Washington School of Medicine
Seattle, Washington

William Caveness, M.D.
Associate Director for Collaborative and
Field Research
National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

Loring Chapman, Ph.D.
Chairman, Department of Behavioral Biology
University of California
Davis, California

John A. Churchill, M.D.
Acting Head, Section on Pediatric Neurology
Perinatal Research Branch
National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

Stewart H. Clifford, M.D.
Project Director & Principal Investigator
The Collaborative Study at the Boston
Hospital for Women, Lying-in Division
Associate Clinical Professor of Pediatrics
Emeritus
Harvard Medical School
Boston, Massachusetts

Elizabeth B. Decker, M.D.
Brookdale Hospital Center
Brooklyn, New York

Murdina M. Desmond, M.D.
Professor of Pediatrics
Head, Newborn Section
Baylor University School of Medicine
Houston, Texas

5

Philip R. Dodge, M.D.
Professor of Pediatrics and Neurology
Head, Department of Pediatrics
Washington University School of Medicine
St. Louis, Missouri

James E. Drorbaugh, M.D.
Project Director & Principal Investigator
The Collaborative Study at the Childrens
Medical Center
Clinical Associate in Pediatrics
Harvard Medical School
Boston, Massachusetts

Robert J. Ellingson, Ph.D., M.D.
Professor of Medical Psychology & Physiology
Nebraska Psychiatric Institute
Omaha, Nebraska

Rudolph Engel, M.D.
Professor of Pediatrics
University of Oregon Medical School
Portland, Oregon

Samuel P. Hicks, M.D.
Professor of Pathology
The University of Michigan Medical Center
Ann Arbor, Michigan

Edward H. Hon, M.D.
Professor of Obstetrics & Gynecology
Yale University School of Medicine
New Haven, Connecticut

Robert L. Isaacson, Ph.D.
Professor of Psychology
University of Florida
Gainesville, Florida

Sherwood A. Jacobson, M.D.
Associate Professor of Neurosurgery
New York Medical College
New York, New York

Arthur Kling, M.D.
Director, Brain Research Laboratory
Department of Psychiatry
University of Illinois School of Medicine
Chicago, Illinois

Schuyler Kohl, M.D., Ph.D.
Professor of Obstetrics & Gynecology
State University of New York
Downstate Medical Center
Brooklyn, New York

Nathan Malamud, M.D.
Chief, Neuropathology Service
Langley Porter Neuropsychiatry Institute
San Francisco, California

Richard L. Masland, M.D.
Professor of Neurology and Chairman of the
Department of Neurology
College of Physicians and Surgeons
Columbia University
New York City, New York

Roger J. Meyer, M.D., M.P.H.
Associate Professor of Pediatrics
Northwestern University School of Medicine
Director, Infant Welfare Society
Chicago, Illinois

Frank A. Oski, M.D.
Associate Professor of Pediatrics
University of Pennsylvania School of
Medicine
Philadelphia, Pennsylvania

Larry K. Page, M.D.
Associate in Neurosurgery
Childrens Hospital Medical Center
Boston, Massachusetts

Warren H. Pearse, M.D.
Professor and Chairman
Department of Obstetrics & Gynecology
University of Nebraska College of Medicine
Omaha, Nebraska

Edward F. Rabe, M.D.
Associate Professor of Pediatrics (Neurology)
Tufts University School of Medicine
Boston, Massachusetts

Joseph Ransohoff, M. D.
Professor and Chairman
Department of Neurosurgery
New York University Medical Center
New York, New York

Frederick Richardson, M.D., M.R.C.P.
Associate Professor of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

Guenter Rose, Ph.D.
Associate Professor of Psychology and Physiology
Nebraska Psychiatric Institute
Omaha, Nebraska

Arthur L. Rosenbaum, M.D.
S. A. Surgeon (R) (T)
Section on Pediatric Neurology
Perinatal Research Branch
National Institute of Neurological
Diseases and Stroke
Bethesda, Maryland

James A. K. Russell, M.D., F.R.C.G.
Professor and Chairman
Department of Obstetrics and Gynaecology
University of Newcastle
Princess Mary Maternity Hospital
Newcastle-upon-Tyne, England

Maria Z. Salam
Assistant Professor of Pediatrics
Department of Children's Neurology
Massachusetts General Hospital
Boston, Massachusetts

S. Mark Sumi, M.D.
Assistant Professor of Pathology and Medicine
University of Washington School of Medicine
Seattle, Washington

Hans-Lukas Teuber, Ph.D.
Professor and Chairman
Department of Psychology
Massachusetts Institute of Technology
Cambridge, Massachusetts

Abraham Towbin, M.D.
Pathologist-Neuropathologist
Danvers State Hospital
Hathorne, Massachusetts
Pathologist (Neonatology)
St. Margaret's Hospital
Boston, Massachusetts

Jack Trembath, M.B., Ch.B.
Research Assistant Professor
University of Nebraska College of Medicine
Omaha, Nebraska

A. Earl Walker, M.D.
Professor of Neurosurgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Lee Willerman, Ph.D.
Research Psychologist
Perinatal Research Branch
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland

Peter O. Yates, M.D., M.C.Path.
Professor of Neuropathology
University of Manchester
Manchester, England

PREFACE

A blow to the head and a subsequent deficit in mentation have been associated since antiquity. The proceedings of this conference on physical trauma and retardation make it apparent that even such a classical sequence deserves examination to distinguish fancy from fact.

The *physical trauma* could include assaults by modalities such as x-radiation, laser radiation and electric shock; it can also encompass the psychologic effects of physical abuse without specific head injury. Early in the planning of this conference, however, it was decided that the two major areas of concern were postnatal and perinatal trauma directly applied to the central nervous system.

Postnatal head injury in children is conservatively estimated by Caveness to involve, annually, 3.3 percent of the population under six years of age, or 794,000 infants and young children. Given a risk of this magnitude, it becomes imperative to define, by long-term studies, such as those of Black, the incidence and nature of any subsequent cerebral dysfunction. Statistically, these concussions, contusions and hemorrhages are an infrequent cause of severe retardation. Behavior and activity disorders, however, appear to be common even in mild injury; here one problem is to distinguish contributing cause from resultant effect.

The evaluation of brain injury due to the forces of labor and delivery is more complex. As pointed out by Adams and others, only subarachnoid and subdural hemorrhages, dural tears, meningeal hemorrhages and spinal cord injury are the acknowledged result of compressive-distortive head injury, yet these phenomena in the neonate have an indefinite relationship to mental retardation. Towbin, as well as Adams, presents considerable evidence for hypoxia rather than mechanical trauma as the common denominator in the vascular events leading to periventricular, cortical and thalamic infarctions that result in the late pathologic changes of gliosis and cavitation, classically but erroneously attributed to traumatic hemorrhage.

If hypoxia is the critical event in the hemorrhagic infarction that results in late sclerosis and cavitation, the next question is the relative role of the direct mechanical forces of labor as a cause of intrapartum hypoxia. The elegant systems of Caldeyro-Barcia and of Hon to monitor the fetal ECG and EEG as indices of intrapartum hypoxia disclose an individual fetal response to the duration and intensity of uterine contraction. This variation may be mechanically explained as due to the direct pressures on the cord or on the head, but more likely it represents a composite response to the forces of labor conditioned by a multitude of factors affecting fetal development. There is an obvious need for such information, obtained from multidisciplinary centers for the study of placental function, fetal development, and intrapartum events.

Regardless of the initiating event, brain lesions induced at early stages of development lead to a pattern of functioning and of anatomic changes distinct from that produced by late lesions. Teuber provides a major review of the experimental and clinical observations of this complex phenomenon, in itself the subject of a recent symposium, *The Neuropsychology of Development,* edited by Isaacson (Wiley, New York, 1968). The definition of the mechanisms that lead to both the sparing of function and to the peculiar behavior seen in certain types of infant lesions might well lead to more rational techniques of training and education.

The avowed purpose of the initial planning conference, held in May, 1967, was to define not only what was known concerning head injury in the pathogenesis of learning disabilities but to formulate the most pressing questions and evoke fresh inquiry of old problems. This assembly of first-class minds giving their concerted attention to the problems of cerebral trauma is a uniquely exciting event, and a tribute to the foresight of the President's Commission on Mental Retardation in planning such a series of multidisciplinary conferences.

Transcription difficulties encountered by the Council for Interdisciplinary Communication in Medicine initiated the unfortunate lag in preparation and publication of the proceedings. Mrs. Susan Meister, Director of the Council for Interdisciplinary Communication, did the initial editing of papers. Appreciation is expressed to Dr. Jack Trembath for assistance in editing the discussions and, most particularly, to Mrs. Marilyn Schlicht, Research Assistant, University of Nebraska, for indefatigably efficient organization of the conference and manuscript.

CAROL R. ANGLE, M.D.

TABLE OF CONTENTS

Page
Participants iv
Preface—Carol R. Angle, M.D. vii

Session I: Introduction

Edgar A. Bering, Jr., M.D.
Hans-Lukas Teuber, Ph.D.

Physical Trauma as a Cause of Mental Retardation
Edgar A. Bering, Jr., M.D. 3
Mental Retardation After Early Trauma to the Brain: Some Issues in Search of Facts
Hans-Lukas Teuber, Ph.D. 7

Session II: Epidemiology

Chairman: Roger J. Meyer, M.D.

The Epidemiology of Head Trauma in Childhood—Introductory Comments
Roger J. Meyer, M.D., M.P.H. 31
Trauma and Mental Retardation
Nathan Malamud, M.D. 35
General Aspects of the Pathology of Cranial Trauma in Infants and Children
Raymond D. Adams, M.D., and Maria Z. Salam, M.D. 53
Discussion 63
Distribution of the Terminal Hemorrhages in the Brain Wall in Stillborn Premature and Nonviable Neonates
Paul I. Yakovlev, M.D., and Remedios K. Rosales, M.D. 67
Postmortem Neuropathologic Findings in Patients with "Birth Injury"
Thomas L. Kemper, M.D. 79
Epidemiologic Studies of Head Injury
William Caveness, M.D. 87

Session III: Perinatal Studies

Chairman: Richard L. Masland, M.D.

Obstetric History of Grossly Retarded Children in the Boston Sample of the Collaborative Study
Stewart H. Clifford, M.D., and James E. Drorbaugh, M.D. 93
Obstetric Trauma in Newcastle-Upon-Tyne
James K. Russell, M.D., F.R.C.O.C., Gerald A. Neligan, M.D., and David G. Millar, M.D. 101

Fetal Head Position During Delivery, and Intelligence
Lee Willerman, Ph.D. 105
Maternal Pelvic Size and Neuropsychological Outcome
Lee Willerman, Ph.D. 109
Neuropsychologic Outcome of Children Born *via* the Occiput Posterior Position
Arthur L. Rosenbaum, M.D. 113
Effects of Intrapartum Uterine Contractions on the EEG of the Human Fetus
E. Garcia Austt, M.D., R. Ruggia, M.D., and Roberto Caldeyro-Barcia, M.D. 117
Obstetrical Factors Influencing Intrapartum Compression of the Fetal Head and the Incidence of Dips I in Fetal Heart Rate
G. Aramburu, M.D., O. Althabe, M.D., and Roberto Caldeyro-Barcia, M.D. 125
Compression Received by the Head of the Human Fetus During Labor
R. L. Schwarcz, M.D., G. Strada-Saenz, M.D., O. Althabe, M.D., J. Fernández-Funes, M.D., L. O. Alvarez, M.D., and Roberto Caldeyro-Barcia, M.D. 133
Discussion 141
Newborn Cerebral Trauma
John A. Churchill, M.D. 145

Session IV: Special Studies of the Developing Brain
Chairman: Ellsworth C. Alvord, Jr., M.D.

Trauma of Labor
Edward H. Hon, M.D. 151
Discussion 161
Trauma to Neck Vessels Leading to Cerebral Damage
Peter O. Yates, M.D., M.C. Path. 167
Discussion 173
Reaction of the Immature Brain to Injury
S. Mark Sumi, M.D. 177
Discussion 188
Effects of Removal of Parts of the Early Infant Rat's Brain on its Morphogenesis and Functional Development
Samuel P. Hicks, M.D., and Constance J. D'Amato, B.S. 191
The Effect of Cerebral Ablation in Infant Monkeys on Motor and Cognitive Function
Arthur Kling, M.D. 197
Discussion 204

Session V: The Premature
Chairman: Schuyler Kohl, M.D., Ph.D.

Premature Infant: Intracranial Hemorrhage and Mental Retardation
C. B. Carlson, M.D. 209

Central Nervous System Damage in the Premature Related to the Occurrence of Mental Retardation
Abraham Towbin, M.D. 213
Discussion 236
The Clinical Evaluation of the Low-Birth-Weight Infant with Regard to Head Trauma
Murdina M. Desmond, M.D., and Arnold J. Rudolph, M.D. 241
EEG in Prematures and Subsequent Development
Rudolph Engel, M.D. 251
Discussion 258
Hematologic Factors in the Premature Infant and Mental Retardation
Frank A. Oski, M.D. 261

Session VI: Postnatal Trauma

Chairman: Charles Barlow, M.D.

Postnatal Trauma: Subdural Hematoma
L. K. Page, M.D., A. D. Rosenthal, M.D., W. D. Morain, M.D., and J. Shillito, Jr., M.D. 267
Definition and Etiology of Subdural Hematoma in Infants and Children
Edward F. Rabe, M.D. 271
Discussion 278
The Battered Child
James S. Apthorp, M.D. 283
Discussion 284
An Interdisciplinary Prospective Study of Head Trauma in Children
P. Black, M.D., D. Blumer, M.D., A. Wellner, Ph.D., J. J. Jeffries, M.B., B.Ch., and A. Earl Walker, M.D. 287
Discussion 288
Intellectual Sequelae in Children and Adolescents Following Prolonged Coma due to Acceleration Concussion
Frederick Richardson, M.D., M.R.C.P. 291
Discussion 292
Summary and Future Plans
Phillip R. Dodge, M.D. 297
Bibliography 301

SESSION I

Introduction

Edgar A. Bering, Jr., M.D.
Hans-Lukas Teuber, Ph.D.

PHYSICAL TRAUMA AS A CAUSE OF MENTAL RETARDATION

Edgar A. Bering, Jr., M.D.
National Institute of Neurological Diseases and Stroke
National Institutes of Health
Bethesda, Maryland

I want to welcome you all and thank you, not only for putting aside important duties to spend the time in these deliberations, but more importantly, for the hard work you have done preparing for this meeting. Dr. Carol Angle, the organizing committee, and the staff of the University of Nebraska also deserve our thanks for their splendid efforts in preparing this conference.

The President's Panel on Mental Retardation, in a report to the President in October, 1962, recognized the facts that mental retardation is not a single disease, is not at present treatable, and is best approached through prevention. This report also contained as one of its recommendations that a series of conferences be held, each relating to one of the several causes of mental retardation. The NIH Staff Group on Mental Retardation, composed of representatives from the NINDS, NICHD, and NIMH, the Children's Bureau, the Office of Education, and the then Vocational Rehabilitation Administration, assumed the responsibility for planning this series of conferences.

The original plan called for seven conferences: Infectious Diseases as a Cause of Mental Retardation, Drugs and Poisons as a Cause of Mental Retardation, Physical Trauma as a Cause of Mental Retardation, Maternal Health and Its Relation to Mental Retardation, Genetic Causes of Mental Retardation, Environmental and Socio-Cultural Factors as a Cause of Mental Retardation, and Legal Aspects of Mental Retardation. The proceedings of the various conferences would be published in similar format, and finally combined into a single volume which would be a reference on the etiology of mental retardation. This plan has been followed with some minor modifications.

This is the fourth of these conferences to be held and the third in the general format of a small closed meeting bringing together representatives from a wide variety of disciplines related to the problem.

The objective of this conference on Physical Trauma as a Cause of Mental Retardation, like the others, is to assemble what is known about this problem so that some estimations can be made about the size of the problem of physical trauma being a cause of decreased brain function or intellectual development, what forms of physical trauma most commonly cause this kind of damage, what are the areas of ignorance related to this problem, and what action might be taken to eliminate physical trauma as a cause of mental retardation; that is to say, what can be done to bring this aspect of mental retardation under control.

14

The planning for this meeting has been much the same as for the others. The first step has been the assembly of a group of scientists identified as being interested and knowledgeable about the problem, where, by discussion, they crystallize the relevant issues and develop general guidelines for the structure of the conference. Following this, a smaller working group has done the hard work of organizing the program and selecting the participants. This kind of thing takes a long time, as you know, and this conference is the culmination of a year and a half of effort on the part of the people involved in planning it.

The first planning meeting for the conference on Physical Trauma as a Cause of Mental Retardation was held at the National Institute of Neurological Diseases and Stroke in Bethesda, Maryland, on May 25, 1967. It included the following people:

Dr. Ellsworth C. Alvord, Jr., University of Washington; Dr. Carol R. Angle, Omaha, Nebraska; Mr. Michael J. Begab, NICHD; Dr. Heinz W. Berendes, NINDS; Dr. Edgar A. Bering, Jr., NINDS; Dr. Loring Chapman, NICHD; Dr. Philip Dodge, Massachusetts General Hospital; Dr. Joseph P. Evans, University of Chicago; Miss Louise Hewson, New York City; Dr. S. A. Jacobson, New York City; Dr. Alan K. Percy, NINDS; Dr. Ralph Reitan, Indiana University Medical Center; and Dr. A. Earl Walker, Johns Hopkins University. Dr. Raymond D. Adams, Massachusetts General Hospital, was unable to attend. Dr. Gerald LaVeck, NICHD, was present for only part of the session.

The entire minutes of this first session are too long to include here, but I will briefly mention some of the major items that emerged.

The problem of definition of mental retardation was of great concern to this group because as was pointed out, the effect of physical trauma on the intellectual capability of an otherwise normal person will relate to their innate capabilities. A genius, knocked off 25 percent, may not be noticeably affected by his injury, but someone who is borderline or low in native capability sustaining an identical injury will end up as a burden to society. Thus, those rendered "mentally retarded" by physical trauma are, in fact, just a special part of the much larger problem of the long-term effects of head injuries on intellectual function. This discussion led to the conclusion that the usual definition of mental retardation was too limiting, and for the development of this conference, the problem should be "the effect of physical trauma as an etiological agent in altering mental development and function." The title of the conference was not changed because of the background of the President's Panel initiating these meetings.

The data available relating to this problem seemed to be rather meagre. Any available data should be tabulated for the meeting and the problem of epidemiology should be brought up.

Considerable discussion evolved around the different periods which would be considered and it was decided to consider three major areas, namely the *prenatal period*, the *period surrounding birth*, and the *period of most active brain maturation* which occurs during the first two years of life. The more mature brain, namely the adult, would be considered only by inference and by those comparisons available.

Another question which concerned this meeting was testing and psychological parameters: not so much methodology, but rather the conclusions that can be drawn from this type of evaluation.

The distinction of physical trauma as opposed to hypoxia or anoxia of the CNS was recognized as a major problem: Is it possible to make such a distinction? How are they related? What is the significance of blood in the spinal fluid at birth? These were identified as major questions for the pathologists.

Finally, they considered possible participants from the various disciplines and launched the smaller final planning committee on its way. The members of this sub-group are: Ellsworth C. Alvord, Jr., M.D., Loring Chapman, Ph.D., John Churchill, M.D., S.A. Jacobson, M.D., and Carol R. Angle, M.D.–Chairman.

Both groups have done their work well and it gives me the greatest pleasure to thank them publicly and officially on behalf of the National Institute of Neurological Diseases and Stroke for their efforts which have produced this conference and insured its success.

MENTAL RETARDATION AFTER EARLY TRAUMA TO THE BRAIN: SOME ISSUES IN SEARCH OF FACTS

HANS-LUKAS TEUBER, Ph.D.
Department of Psychology
Massachusetts Institute of Technology
Cambridge, Massachusetts

The mandate for this group, as I understand it, is to define the extent of the problem of mental deficiency resulting from early brain trauma. We should arrive at some educated guesses about its frequency and get a better understanding of the precise etiology of post-traumatic intellectual changes; if possible, we should suggest countermeasures designed to reduce the incidence of this tragic condition.

As if this were not enough, or already too much, to consider in three days, at the present stage of our knowledge, there are several subsidiary questions that should be asked as well: Are there particular aspects of the pathophysiology of early brain damage that make it different in its effects from similar tissue-damage sustained later on? Is the common claim valid that early damage tends to be less disabling than corresponding lesions at maturity? And, lastly, and often overlooked: Is there some beginning of insight into the *nature* of behavioral change after early lesions? Can it be distinguished, qualitatively, from effects of later lesions, on the one hand, and from mental retardation due to other causes, on the other?

All this is so difficult and uncertain that one is tempted to begin this conference in the way DuBois-Reymond (1872) ended a famous address on the limits of the natural sciences: "*Ignoramus–Ignorabimus!* We don't know, and we shan't know!" Yet, I propose here at the outset that if we try to pool what each of us knows, we may come up with at least the beginnings of an answer to most of the questions just raised; even if the conference ends, as it well might, with a collective *ignoramus*, it should not end with an *ignorabimus!*

Range of Problems

In order to make sure that it does not, we had better define at this early stage the impressive scope of our present ignorance. Strictly speaking, we do not know what role is played by physical trauma in mental retardation, because we

---

Preparation of this survey article was facilitated by the following grants (which also supported the work at M.I.T. reported here): NIMH Program Grant #05673 to the author, a Clinical Research Center Grant #FR88 to M.I.T., and a grant from the John A. Hartford Foundation of New York to the M.I.T. Psychophysiological Laboratory.

cannot ascertain the total incidence of trauma, or define which subsets of those children who have early trauma, have mental retardation as a consequence. Differently put, the set of children who exhibit mental deficiency *without* any history or independent evidence of cerebral trauma may include, in fact must include, an unknown number of those whose retardation is actually due to trauma. Conversely, there are strong arguments from clinical experience and, even more, from laboratory studies suggesting that some early lesions are not followed by mental retardation, or, for that matter, by any detectable behavioral deficits.

This conference cannot define these various sets of children because the data are lacking (cf. Sabina Strich, 1969): It is by definition impossible to estimate the incidence of undetected damage. There does not yet exist any *systematic neuropathology* of early brain damage; at best, a serious bias is bound to operate: we are inclined to study the brains of children who combine obvious lesions (i.e., cerebral lesions, evident while alive) with equally manifest behavioral deficits. Many of these children are particularly accessible, because they happen to be institutionalized.

We shall return to these vexing problems of sampling later on, after considering some of the data from experiments on young animals. If early lesions need to be larger or more diffuse than corresponding lesions in adults in order to be detected during life, then we undoubtedly commit both kinds of errors, in our effort at achieving clinico-pathologic correlations: we miss early lesions that did not produce deficiency, and we interpret some deficiency as due to early lesions that may have been purely coincidental.

Faced with these difficulties, we shall limit ourselves for the time being to what we called the subsidiary questions. It is really true that early lesions are less disabling than corresponding lesions sustained later in life? The answer may differ depending on the kind of early lesion, its site and size, but, as we shall see, it might also differ depending on the kind of behavioral tests applied (Teuber and Rudel, 1962). Thus, we need to look at the "when" and the "where" of the lesions, and, just as carefully, at the "what," that is, the nature of the ensuing behavioral change.

We are also well advised to take up these questions separately, first for the work on experimental animals, and then for observations on man, because the results, at least superficially considered, appear to be rather different. Explorations of the effects of early lesions in animals have added up to the deceptively simple conclusion that early removals of cerebral tissue have less effect upon performance than later removals. This conclusion is eminently teachable but is it true? In man, certain early lesions have, at times, been claimed to be *more,* rather than less disabling, as compared with similar lesions incurred at maturity (e.g. Hebb, 1942, 1949; Russell, 1959). Is the seemingly different picture one gains from working with our own species a reflection of the difference in lesions (ill-localized, but often large and multiple in man), or in the rather narrow range of tests employed in the experimental animals? How general are the findings in animals, and how far can one extrapolate in this instance from subhuman species to ourselves?

I. Observations on Animals with Early Cerebral Lesions

Experimentation with early cerebral ablations in animals, from circumscribed regions—the question of "when" and "where" got its major impulse from the work of Margaret Kennard, in Fulton's Laboratory at Yale, in the thirties and forties (1936, 1938, 1942). Placed strategically down the hall from a project on experimental obstetrics involving rhesus monkeys, under Mrs. van Wagenen, Margaret Kennard found herself with an ample supply of newborn macaques, in which she could compare the effects of removing the motor cortex at birth or soon afterwards, with the effects of corresponding removals performed on older monkeys.

Motor Cortex

The results seemed to indicate a considerable difference in the severity of the ensuing deficits. Maintenance of posture and locomotion, including climbing and jumping, was still possible in monkeys with early removals, but badly impaired in the animals that had incurred the removals at maturity. The results were complicated by the fact that some of Margaret Kennard's protocols pointed to certain delayed effects of early lesions, such as delayed appearance of spasticity. There also were difficulties of interpretation due to the initial lack of histologic reconstruction of these experimental lesions, coupled with a tendency to assume, without further proof, that the relative sparing of function in animals with early lesions was due to some form of "re-direction of dendrites" (an hypothesis advanced by Margaret Kennard as a special instance of "neurobiotaxis)."

Visual Cortex

Nevertheless, Kennard's basic observations on the motor cortex were subsequently extended to several other cerebral systems. Doty (1961) was able to show what looked like complete survival of visual pattern and depth perception after removal of striate cortex in neonatal kittens, (quite in parallel to the earlier reports of Tsang (1937 a, b), who had seen a relative sparing of maze learning and of pattern vision after visual cortex removal in very young rats.

These results were so difficult to accept that some of us questioned the completeness of the lesions in Doty's animals. One expects that after complete striate cortex destruction, all of the lateral geniculate body should be degenerated. Yet, there seemed to be some viable undegenerated remnants of this structure in at least some of Doty's kittens. Similarly, questions were asked about the scope of the experimental tasks that had been used in establishing the claimed integrity of visually-guided behavior. However, Tucker and Kling (1966) were able to supplement Doty's observations by making even more extensive lesions in newborn kittens (removing striate as well as prestriate cortex, bilaterally), and demonstrating the survival of capacity for discrimination of temporal patterns, on a task involving successive comparison of long and short flashes of light.

Auditory Cortex

This task had been constructed in direct analogy to an auditory task used in a now classical demonstration by Diamond and Neff (1957), who have proved, for adult cats, that discrimination of tonal patterns was abolished after extensive ablation of auditory cortex, even though intensity and frequency discrimination as such remained intact. The survival of the cat's ability to discriminate tonal durations, in spite of large auditory-cortex removals inflicted soon after birth, has been shown by Sharlock, Tucker, and Strominger (1963). They were thus able to extend Doty's evidence and their own, for the visual system, to the auditory cortical projections: early destruction of these projections, in the kitten, left a capacity intact that seemed irrevocably lost if the same lesions were made in the adult animal.

SOMATOSENSORY CORTEX

Similarly, tactile-kinesthetic capacities have been tested in kittens and cats by Benjamin and Thompson (1959), who compared performance on various sensory discriminations following early and late bilateral removals of somatosensory cortex. Their study is particularly impressive because it was one of the first to provide us with detailed histologic reconstruction of the thalamic aspects of the lesions. These reconstructions showed that patterns of thalamic degeneration were essentially identical after early and late removals. Yet, the functional consequences were radically different: The early removals spared capacity to perform on all but the most difficult sensory discrimination tasks; the later removals by contrast, produced animals that failed all of the tasks applied.

Kennard's initial claims about relative sparing of motor function after early cortical lesions had thus been essentially vindicated by experiments on visual, auditory and somatic-sensory cortex. The question remained: could these findings be extended to more complex tasks where solution in the adult animal seems to depend on the integrity of so-called "association cortex," or to those aspects of behavior (admittedly ill-defined) which are deranged by invasion of certain allocortical and subcortical structures?

FRONTAL GRANULAR CORTEX

In the adult monkey, bifrontal lobectomy (as well as certain fractional bilateral removals of frontal cortex) interferes permanently with the animal's capacity to acquire or relearn delayed-response and delayed-alternation tasks (Jacobsen, 1935). It was therefore a far-reaching extension of Kennard's principle when Harlow and his co-workers discovered that early lesions in the frontal lobes of the rhesus monkey did not seem to impair delayed-response capacity (Akert et al., 1960; Harlow, Akert & Schiltz, 1964). In normative studies, Harlow had been able to demonstrate that capacity for delayed-response performance appears in the full-brained monkey at around 120 days after birth (Harlow, 1959); it becomes fully established only after 200 days of age or more. If a bifrontal lobectomy is done before the age of three months, the capacity to perform the task appears all the same, and essentially at the age normal for the emergence of the capacity. These results have been confirmed by Tucker and Kling (1967; see also Kling & Tucker, 1968).

More recently, however, Harlow and his colleagues have been able to show that this sparing of delayed response cannot be extended to all other tasks that are sensitive to similar lesions inflicted later in life: a particularly taxing test, which Harlow calls "oddity learning set," is impaired at all ages, regardless of when the lesions are produced (Harlow et al., 1968). It appears, therefore, that one gets evidence for sparing or loss of capacity after early lesions in the monkey's frontal lobes, depending on the nature of the task employed. There is a further and curious trend in Harlow's most recent results: there may be an age of maximum vulnerability (perhaps 12 months in the macaque) for certain tasks and certain lesions. After that age, the effect of the lesion, although clearly more disabling than effects of very early ones, are again less severe (Harlow et al. 1968, and personal communication).

POSTERIOR "ASSOCIATION CORTEX"

It is well known that removal of frontal "association" cortex, in the adult monkey, has behavioral consequences quite distinct from removals of so-called posterior "association" cortex, i.e., the parieto-tempero-occipital sector (Blum, Chow, and Pribram, 1950). The frontal lesions produce the deficits just described, such as losses on delayed-response and delayed-alternation tasks, whereas certain posterior removals, involving the inferolateral temporal neocortex, result in severe deficits in visual discrimination learning (originally shown by Kluver and Bucy in 1939 and then explored by means of fractional lesions, see Mishkin, 1954; Mishkin and Pribram, 1954; Riopelle, Harlow, Settlage, and Ades, 1951). We have described such contrasting consequences of different cortical removals as instances of "double dissociation of symptoms," whereby one capacity is lost with one lesion, and another capacity with another (Teuber, 1955). Early bilateral removals of temporal neocortex in the monkey have now been shown to leave visual object discrimination essentially intact, under test conditions that are adequate to demonstrate severe impairment after late lesions in the same lateral and inferior neocortical areas of the monkey's temporal lobes (Raisler and Harlow, 1965).

"LIMBIC" STRUCTURES

In spite of this additional instance of "sparing of function," after early lesion, one might expect a different outcome, if the lesion encroached on mesial temporal structures, such as the amygdaloid complex and the hippocampus, or other allocortical portions of the so-called "limbic" system. In point of fact, the picture here is not too dissimilar from that obtained after neocortical ablations. Early destruction of tissue in the amygdaloid complex (Kling, 1962), in very young kittens, does not seem to be followed by the changes in affective behavior that one often sees after similar destructive lesions in the adult animal, and Isaacson and his colleagues have recently obtained analogous results after bilateral hippocampal removals in very young kittens as compared with older cats (Isaacson, Nonneman and Schmaltz, 1968).

These experiments are particularly significant for our topic since lesions of the hippocampal zone in the human adult have been followed by extremely grave deficits in the learning of new material, amounting to an anterograde amnesia (Milner, 1966). Admittedly, the situation is less clear after corresponding removals of hippocampus in experimental animals (see Douglas, 1967; Milner loc. cit.; Milner and Teuber, 1968) but it remains true that there are a number of behavioral tasks that are sensitive to hippocampal removals in adult rats and cats, and that could be applied in young animals after corresponding removals made early in life.

The tasks used by Isaacson and his colleagues comprised a runway problem, a visual discrimination and reversal learning test, and various operant conditioning schedules (DRL schedules), in which the animal has to wait a certain number of seconds between bar presses in order to obtain its reward. Thus, on a "DRL-10" schedule, an animal must wait 10 seconds after each bar press in order to obtain reinforcement; if he presses to soon, he is not rewarded, and a timer is re-set automatically for a new 10-second delay period. Performance on all three types of tasks, the runway, the discrimination learning series, and the DRL-schedules, is altered by hippocampectomy in adult animals, although any unitary interpretation of these deficits, in terms of some underlying alternation in behavior, is still in doubt (see Douglas, 1967). After bilateral hippocampectomies done in very young kittens, however, performance on two of the three tasks (runway and discrimination learning) appears unaffected; only the third task, requiring the DRL 10 schedule of operant conditioning, is as clearly sensitive to the early lesions as it is to those inflicted on a mature animal (Isaacson et al., 1968). We thus have a result for early limbic lesions that corresponds rather closely to Harlow's more recent results for early frontal removals: Performance on some tasks is unaffected by early lesions but clearly impaired by later removals; performance on certain other tasks, however, seems equally impaired by lesions at either stage, early and late. Yet, several questions remain.

One would like to know whether the tasks that are equally affected by early and late lesions owe their sensitivity simply to the fact that they are more difficult to master at any age, or whether they involve, instead, qualitatively different aspects of behavior than those tasks that are only affected by later removals. Apparently, no task has been identified, so far, on which animals with early lesions would fare worse than animals with similar lesions imposed later on.

SUBCORTICAL STRUCTURES

Furthermore, one would like to know whether an extension of the range of studies on early lesions in animals to deeper, subcortical systems of the brain might give different results: Is there less sparing with such deep lesions than after the neocortical and allocortical ablations that have already been explored? Only a few steps have been taken in this direction. Thus, Kling and Tucker (1967, 1968) have inflicted combined lesions of the caudate nucleus and of lateral frontal cortex on very young monkeys; either lesion alone, in the adult, will interfere with delayed-response and delayed alternation tasks (Battig, Rosvold, and Mishkin, 1960; Rosvold and Delgado, 1953; Teuber and Proctor, 1964). The combined frontal-caudate lesion inflicted early in life did abolish delayed-response capacity entirely; beyond that, animals with this combined lesion were extremely difficult to maintain; they could not be left to be reared by their mother, showed retardation in growth, and developed seizures and marked hyperactivity at 5–6 months of age.

This congeries of symptoms, after early combined fronto-cortical and caudate lesions, is impressive, though it is difficult to say how one should interpret the loss of delayed response amongst all of the other grave and debilitating symptoms. Hyperactivity has long been known as a consequence of caudate lesions in adult monkeys (see Davis, 1958) but its delayed onset after early lesions is of considerable interest, since it provides a parallel to some especially salient clinical phenomena seen after early head injury in children (Black, 1969). Obviously, much more work should be done on the consequences of subcortical lesions in very young animals, by recording effects of subcortical lesions alone, and of subcortical lesions in combination with cortical ones, since it is far from clear whether it is the subcortical locus of lesions that leads to loss of function after early injury, or whether this loss requires that lesions at different levels of the neuraxis must always be combined.

The Role of Plasticity

Lastly, we are still far from an understanding of the basis for any sparing of function that does occur after early cortical lesions in animals. Is it due to some process whereby remaining structures—possibly subcortical ones—can assume functions "vicariously," i.e., assume functions which they would not ordinarily perform, as has often been claimed? Or is there an abnormal anatomical plasticity, of the sort proposed by Margaret Kennard (1942)?

There are virtually no data on these questions, except for the beautiful studies in rodents by Hicks (which will be presented later on in this conference) and some very recent disclosures by Gerald Schneider, from our departmental laboratories at M.I.T., on the hamster. Schneider has shown (1967, 1969), as have several others in recent years (e.g., Diamond, 1967; Hall & Diamond, 1965a, b; Humphrey & Weiskrantz, 1967) that the mammalian visual system includes at least two parallel and largely independent pathways: one is the classical retinogeniculo, calcarine pathway from the eye to the striate cortex; the other is a path from the eyes to the tectum and thence via the lateral posterior nucleus of the thalamus to the pre-striate cortical regions. Considerable experimental evidence suggests that the logic of "double dissociation" (Teuber, 1955, 1959) might be applied to these two systems, since destruction of visual cortex, in the adult hamster, abolishes capacity for discrimination of visual patterns but leaves simple localizing responses to visual targets intact, whereas lesions of the superior colliculi abolish the localizing responses but not those to visual patterns (Schneider, 1967, 1969. It is as if the classical retino-striate system were involved in telling the animal "what" it sees, and the retino-collicular system, "where."

These studies are being extended to very young hamsters. By destroying the superficial layers of the superior colliculi in newborn hamsters, Schneider and Nauta (1969) were able to demonstrate that some fibers from the retina that would normally terminate in the upper layers of the superior colliculi, (Schneider, 1968), now synapse instead in other areas, such as the lateralis posterior group in the thalamus. Such a selective redirection of fibers is doubly startling, because it shows appropriate affinity for the system to which the fibers "belong," and suggests experiments on the behavioral aspects of early lesions in either portion of the visual system, the geniculo-striate or tectal pathways. Behaviorally, hamsters with neonatal lesions in the roof of the midbrain fail to show the disorder of localizing seen after the same lesion imposed on the adult animal, so that, in this instance, sparing of function may well reflect a true plasticity of anatomical connections.

But how far can this paradigm be extended to other functional systems and other species? There are suspicions of some postnatal "repair" of hippocampal tissue in cats, after the drastic lesions inflicted on this structure soon after birth (see Isaacson et al, 1968), but the anatomical picture in these animals is far from clear, and the hippocampus is known to continue its differentiation quite normally for several days after birth at least in rats (see Altman and Das, 1965), and mice (Angevine, 1965). As Isaacson and his colleagues point out, one needs radioneurographic studies after lesions inflicted on very young brains in order to evaluate the old claims for a compensatory hypertrophy of neuronal elements in response to early cerebral lesions.

Whatever the mechanism, the preponderance of evidence is still strongly in favor of the original Kennard principle. At least for restricted cortical removals, it is true that early lesions are less descriptive of subsequent performance than later lesions, although we still do not know why this should be so. Even less is known about the question of "where," i.e., the site of lesion and possible role of subcortical structures, and least of all about the question of "what," i.e., the nature of those aspects of performance that are lost or spared following earlier and later lesions. Much of this trouble derives from the limited scope of the tasks that have been applied in the animal laboratory and from the difficulties of their interpretation.

II. Observations on Early Lesions in Man

The handicaps which beset the work on early trauma in our own species are almost the opposite of those encountered in current work on subhuman forms. In man, the "when" of the lesion is often incompletely known, and information on site and size of lesions—the question of "where," becomes available only for small and, as we have pointed out, seriously biased samples of cases. On the other hand, much more could be done in our own species about exploring the *nature* of performance after trauma, the questions of "what" it is that is disturbed, and about the true quality of those aspects of function that seem to be preserved.

To anticipate, at the outset, the main conclusions I hope to reach with the survey that follows, "sparing" of functions after early lesions in man often turns out to be achieved at a price: some functions are probably unaffected after early lesions (just as in animals), as compared with lesions sustained at maturity, but in these same cases of early trauma, there are other aspects of human behavior that suffer either as much as if the lesion were incurred later on, or actually, more (Teuber and Rudel, 1962). Evidence for this sort of summary statement is admittedly fragmentary, but deserves review because the fragments, if considered together, suggest outlines of a more coherent picture.

Congenital Absence of Commissures

The traditional view that early lesions in man, as in animals, are less effective than later ones, is based primarily on two groups of observations. In the first group, we have the frequently mild or even undetectable consequences of *congenital absence* of certain brain structures, such as the corpus callosum. In the second group are the numerous clinical impressions of relatively mild and transient aphasias or hemipareses after cerebral insults in children, as contrasted with the much more severe and protracted course of similar conditions in adults. On closer inspection, however, both sets of observations turn out to imply more than is ordinarily assumed.

Congenital absence of the major interhemispheric commissures is not infrequently diagnosed during life on the basis of radiologic findings. Some uncertainty clings to such a diagnosis, either with regard to the completeness of the supposed congenital absence of these large fiber systems, or, conversely, with regard to the claimed selectivity of the developmental deficit, since absence of the callosum is often associated with other cerebral anomalies. Nevertheless, most observers agree that patients with presumed congenital absence of the corpus callosum tend not to exhibit anything approaching the severe disconnection syndromes that one often sees after surgical division of the callosum in adults (Ettlinger, 1968; Gazzaniga, 1968; Jeeves, 1965; Sperry, 1966).

Ongoing studies at the Maudsley Hospital in London under Dr. G. Ettlinger suggest that cases of supposed congenital absence of the callosum show no particular difficulties in transferring sensory information from one side of the body to the other, much in contrast to the patients with commissurotomies performed in adulthood (see Sperry, 1966). In a detailed study of a single case of congenital absence of the callosum, Gazzaniga (1968) was able to demonstrate one symptom of disconnection—a failure to imitate passively imposed postures of one hand with the other hand, whereas many other, similar tests for disconnection in the visual and tactile sphere were negative. Such a relative sparing of interhemispheric functions in human cases of congenital absence of the corpus callosum is all the more paradoxical because early callosal transections in monkeys apparently lead to disconnection syndromes that are not too different from those seen in older animals with the same operation performed in adulthood (Yamaguchi & Myers, 1969).

Whatever the status of specific interhemispheric transfer functions in congenital absence of major commissures, there is a suspicion of additional effects of such maldevelopment: superior intelligence is rarely found in such cases. The preponderantly low intelligence quotients might conceivably reflect the consequences of other anatomical anomalies which are so frequently associated with congenital absence of the callosum. However, another possibility must also be borne in mind: Early absence of commissures might interfere less than later transection with information flow between the hemispheres, but it might carry another and more subtle penalty, manifested in a more general reduction of intelligence.

EARLY LESIONS OF LANGUAGE AREAS

Similar doubts cling to the observations on recovery from aphasia in children: such instances do not necessarily mean that there is a complete restitution to the premorbid level, since rather specific learning deficits tend to remain. Cases of this sort deserve much fuller documentation than they have received, although it is certainly true that massive lesions of the left hemisphere have a different prognosis as to language functions, depending on *when* the damage is sustained. Even massive damage to a left hemisphere at birth or in the first few months after birth need not interfere with the development of some language.

This observation is usually interpreted as an especially clear instance of flexibility of functional representation in the infantile brain, but the flexibility may require a curious trade-off. Dr. Brenda Milner has recently surveyed all of the hemicorticectomies performed at the Montreal Neurological Institute (1968). These removals were undertaken for relief of otherwise intractable epilepsy arising from a cerebral hemisphere badly damaged at birth or soon afterward. Bearing in mind that this is a rather special group of cases, two of Dr. Milner's findings should be particularly noted: In her series of cases, language did not develop in the right hemisphere unless the early lesion in the left encroached upon the language zones (as defined by Penfield and Roberts, 1959). Moreover, the average intelligence quotients in those patients whose speech developed definitely in the right hemisphere was rather low, suggesting that the sparing of expressive language in the face of early lesion to a dominant lobe might have been achieved at a price.

Early Hemisphere Specialization

Unfortunately, there are still no definitive studies contrasting the intellectual status of children with right and with left hemiparesis after early damage to the corresponding cerebral hemispheres. Some work carried on for a number of years in our own laboratories (by Drs. Maria Wyke, Rita Rudel, T.E. Twitchell and me) suggests that the plasticity of the young brain may have been overrated. Although language does develop regardless of large unilateral damage to the left or right cerebral hemisphere, children with hemiparesis tend to exhibit an attenuated version of the adult pattern of symptoms: i.e., predominantly verbal difficulties after left-hemisphere involvement, and, reciprocally, certain nonverbal difficulties, such as trouble with spatial relations, perception, construction, and memorizing for visual patterns, after right-hemisphere lesions.

Do global intellectual changes encompassing both clusters of symptoms require bilateral lesions of the convexity, or, equivalently, more deepseated damage in the midline? In the absence of adequate clinico-pathologic correlations, we cannot tell, but we can pursue the study of the nature of the deficits found after early lesions in greater detail, holding the questions of specific localization in abeyance. As more neuropathologic observations accumulate, the gaps in the picture may close, particularly if we have a better grasp of the qualitative aspects of the deficits found after early lesions in man.

Accordingly, I shall devote the balance of this paper to a review of a series of ongoing studies on brain-injured children, carried out in our own laboratory, and oriented primarily toward the problem of analysis of residual function. This work proceeds in collaboration with Dr. Rita Rudel and Dr. T.E. Twitchell; it takes its departure from an earlier series of studies that has been published (Teuber and Rudel, 1962) and hence will be treated summarily here. Only small portions of the new series have been reported elsewhere; I shall therefore attempt a somewhat more detailed synopsis of this ongoing work.

Effects of Early Lesions on Three Perceptual Tasks

In the earlier study, there were 72 children—36 boys and 36 girls—ranging in age from 4 years 11 months to 18 years. Although all were diagnosed as having sustained perinatal injuries resulting in cerebral palsy, their motor impairment ranged from barely detectable to severe. Three perceptual tasks were given to these children: On one (adjusting a sound source to the apparent overhead position under conditions of body tilt), there were no differences between these brain-damaged children and normal control subjects matched for age; differences appeared only after the age of eleven and then increased as one went from younger to older groups.

On a second task involving "starting position effects," the error of the brain-injured children exceeded that of the matched control groups at all ages. Here, we assessed the degree to which a child's setting of the sound source would fall short of the true midline, as a function of the initial position of the source: if it came in an arc from the child's left, there would be a tendency to set it too far to the left of the midline, and correspondingly for starting positions on the right. Lastly, on a third task—that of righting oneself from a tilted position, under exclusion of vision, there were differences between brain-injured children and control subjects below the age of eleven, but no such differences could be detected beyond that age (fig. 1).

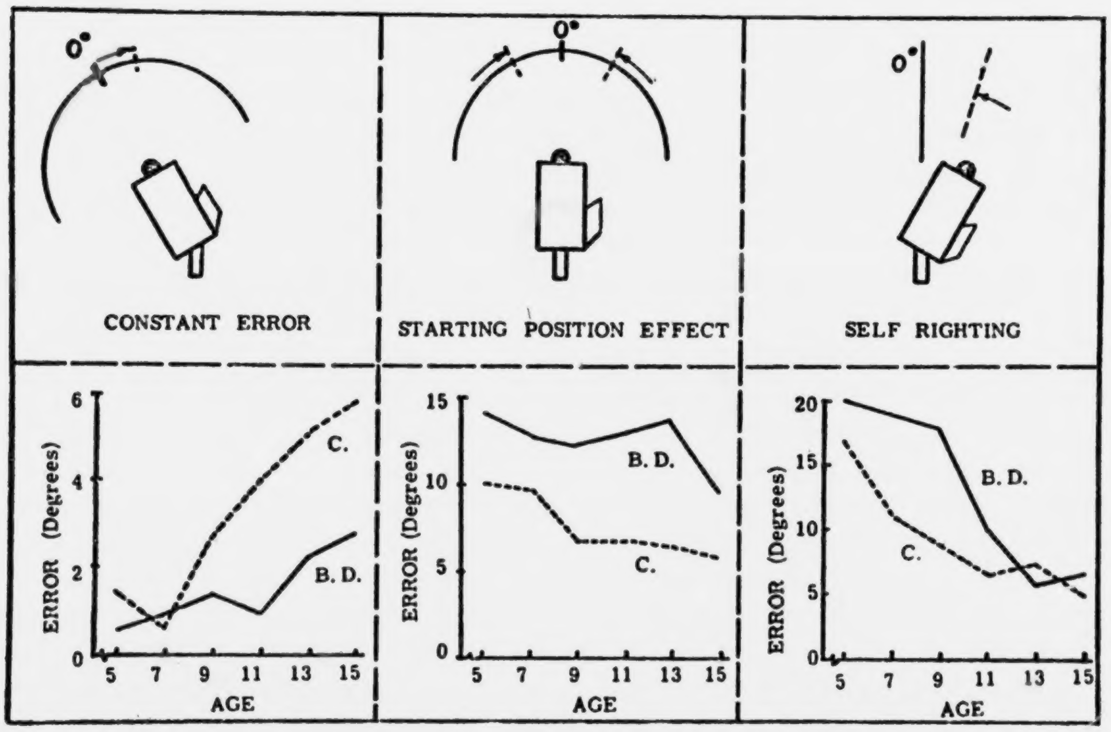


FIGURE 1.—Three closely related experimental tasks (above) on which children with perinatal brain damage perform as indicated (below). On the first task (left), a difference between brain-injured and normal children emerges only at later ages; on the second (middle), the difference is apparent at all ages, and on the third (right), the difference is evident for the younger children, but disappears when older children are tested (based on Teuber and Rudel, 1962). For further details, see text.

The results, although derived from limited and obviously artificial laboratory tasks, suggested that one may have to approach the question of early lesions in man with some care: instead of asking, simply whether early lesions are less disruptive of functions than later ones, one should consider (1) those aspects of behavior for which effects of early lesions appear only with a delay (as foreshadowed in some of Kennard's incidental observations on delayed onset of symptoms); (2) those aspects of behavior that are clearly impaired at all ages after early lesions, and (3) those aspects where an effect of early lesions is noticeable in the first few years, but becomes undetectable as development progresses.

NEUROLOGIC STATUS AND SPECIAL SENSORY TESTS

Put in this fashion, the results of our earlier study can be said to have provided a framework for our current work, in which we are trying to tie the observations on behavioral changes in children with early brain trauma to their individual neurological status. These investigations involve repeated testing for five years, of 63 children, ranging in age from 7 to 17, all with clear history of perinatal damage to the brain. The children, however, are all considered sufficiently educable to attend special schools in New York City, and their present neurologic symptoms are for the most part minimal, consisting primarily of reflex changes in one or several extremities, and other anomalies of their motor development (see Twitchell, Lecours, Rudel and Teuber, 1966).

It is, of course, impossible to offer anything but guesses about the neuropathology involved, but these children seem rather typical of those usually described as mildly brain-injured, although not necessarily as falling under the ill-defined classification of "cerebral palsy." They were subjected to detailed neurologic examinations, and to many of the tasks which our laboratory had previously used in studying the effects of later trauma in adults with missile wounds of the brain. We can therefore contrast our observations on these children to those made in adults with late injuries, and can compare results for either group with those derived from animal experimentation, fully realizing that the lesions in any of these groups may not be comparable to those in the others.

To begin with findings on visual and sensory deficits, only two of the 63 children with early trauma in this new study had visual field defects (both had hemianopias), whereas there were 48 cases of visual field defects in 232 consecutive cases of penetrating brain wounds incurred in adulthood. Furthermore, none of the 63 children had impaired cutaneous sensitivity as tested by detection of light touch (graduated nylon filaments), and there were no instances of diminished capacity for resolution of two compass points simultaneously applied to the palm, nor of disorders of punctate localization. These essentially negative findings in children with definite reflex changes and other motor signs pointing at consequences of their early brain trauma, are all the more surprising since adults with penetrating brain trauma incurred in adulthood show frequent and definite losses of tactile sensitivity on one or several of the same quantitative tasks. In a survey of 121 such cases, selected only for the presence of a penetrating brain wound, nearly two-thirds of the sample has abnormal tactual thresholds (Semmes, Weinstein, Ghent and Teuber, 1960). These results might mean either that the cases in the younger and older groups were not comparable, or that there is in fact less vulnerability of certain sensory functions after early cerebral lesions in man.

HYPERESTHESIA

The rarity or absence of sensory losses after early lesions suggest (but do not prove) some quantitiative difference between effects of early and late injury; in addition, there now is evidence for a qualitative difference, since there is a sensory symptom derived from early lesions that we have not so far seen in cases of brain injury incurred later in life. Repeated tests of tactile sensitivity, over several years, in the group of 63 children with perinatal brain damage, have revealed that nine of these children have a definite hyperesthesia, i.e., an abnormally increased sensitivity (Rudel, Teuber and Twitchell, 1966). Eight of these nine children shown abnormally "good" two-point resolution, in addition to the abnormally increased pressure sensitivity (measured by calibrated nylon filaments, in the fashion of von Frey hairs).

Much remains to be done to test the implications of this finding. Are there similar instances of hyperesthesia after early lesions involving the auditory or visual systems? Is the nature of this hypersensitivity comparable to that seen permanently on the skin of amputation stumps (Teuber, Krieger and Bender, 1949; Haber, 1955) or to that claimed to appear transiently after certain types of sensory deprivation (Milner and Teuber, 1968; Zubek, Flye and Aftanas, 1964)? We cannot tell, but the results suggest a systematic search for further qualitatively different effects of early *vs.* late lesions.

COMPLEX TACTUAL TASKS

The picture changes again when we turn from elementary to more complex achievements of somatic sense: there the relationship between early and later lesions seems to be reversed. In the adult group (Semmes et al., 1960), elementary tactile disturbances were more frequent than were disturbances in the discrimination of complex patterns presented to the tactile-kinesthetic modality. Recognition by palpation of bi- and tridimensional forms was not as often affected as were sensory thresholds, and when pattern recognition had suffered, this happened predominantly in association with threshold changes, i.e., losses in elementary sensitivity (see Teuber, 1959, for summary). Conversely, in the sample of children with early lesions where there were no abnormal thresholds (except for hyperesthesia), form recognition by palpation was grossly abnormal in more than half of the cases. This loss on tactual pattern tests was still found when the children with early brain damage were matched against control subjects of the same mental (rather than chronological) age (Rudel and Teuber, unpublished).

Such results (and there may be analogous ones for vision, and probably for audition) are compatible with the view that early lesions can produce a relative sparing of elementary aspects of performance at the expense, so-to-speak, of performance on more complex tasks. This impression is reinforced if one further broadens the basis for comparisons between the early and late lesion cases. We have done so (Rudel and Teuber, 1969) by applying tasks involving spatial orientation; these tacks had previously been shown to be sensitive to parietal and frontal lesions after brain injuries sustained in adulthood. Performance on these tasks is grossly impaired in our brain-injured children, and clearly more so than in the adults.

TASKS INVOLVING SPATIAL ORIENTATION

On a test of spatial orientation involving route findings in a large laboratory room, by means of a series of maps (Semmes, Weinstein, Ghent and Teuber, 1955; Teuber, 1966), only men with parietal-lobe penetration had shown significant deficits, in the previous studies on the effects of combat wounds of the brain. The same task was given to our children with perinatal brain damage, with the result that there were profound deficits for nearly all of them. These deficits were still evident after the group with early brain injury had been matched against a much younger control group so that the average mental age of the brain-injured children was two years *above* that of the control group. Again there was a qualitative difference, and not only a quantitative deficit in the performance of the brain-injured children, as compared with their controls: the brain-injured children rarely walked along diagonal paths, regardless of whether such diagonals were required by the maps or not. In fact, 15 of the brain–injured never walked a single diagonal, a peculiarity we had not seen in any of the control subjects (Rudel and Teuber, 1969a).

Similarly striking differences between early and late-lesion cases appeared on a test that disclosed deficits of slightly different kinds after parietal and after frontal lesions sustained in adulthood. This test involves orientation to a schema of the human body, requiring the patient to point to those parts of his own body that correspond to parts marked on a diagrammatic picture of a man placed in front of him (fig. 2). The task (an extension of Henry Head's Eye-and-Ear Test) also requires rapid and repeated mirror-reversals in orientation since successive cards bear pictures of the human body seen from the front or back (Semmes, Weinstein, Ghent and Teuber, 1963; Teuber, 1966).

On this test, adults with parietal lesions fail by virture of what seems to be a general difficulty with orientation to the body, whereas patients with frontal lesions probably fail mainly because of a specific difficulty with the required rapid reversals of right-left orientation. Children with early brain lesions fail in both ways, as if their deficit were more global, as well as more severe than the late-acquired deficits of the adults (Rudel and Teuber, 1969).

USE OF NON-SPECIFIC TESTS

Our earlier work with adults had led to the identification of certain tasks on which injury in any lobe, and in both hemispheres, appeared to produce some lasting deficits (Teuber and Weinstein, 1956, Teuber and Liebert, 1958). The clearest example of such a non-localizing or non-specific task was a test based on a procedure devised by Gottschaldt (1926, 1929), in which one has to detect a figure within an array of embedding lines. Men with penetrating brain wounds incurred in adulthood did badly on such tasks, regardless of whether their injury fell into the right or left hemisphere, or into the frontal, parietal, temporal or occipital lobes. These results have recently been confirmed elsewhere in groups of adult patients with brain lesions of quite different etiology, in whom the damage was due to vascular or neoplastic disease (Vignolo, 1969, in press). In this more recent study, as in our earlier one, patients with aphasia did particularly poorly, even though the task appears to be non-verbal.

Given such a non-specific sign of convexity damage in the adult, it is reasonable to expect that early lesions might produce similar impairment, and this is, in fact, the case. Rudel and I could show (1962) that hidden-figure tasks of this type were done poorly by children with early brain lesions, irrespective of the age at which they were tested, and over a rather wide range of similar tasks.

Variations of this approach have been introduced by Cobrinik (1959), who

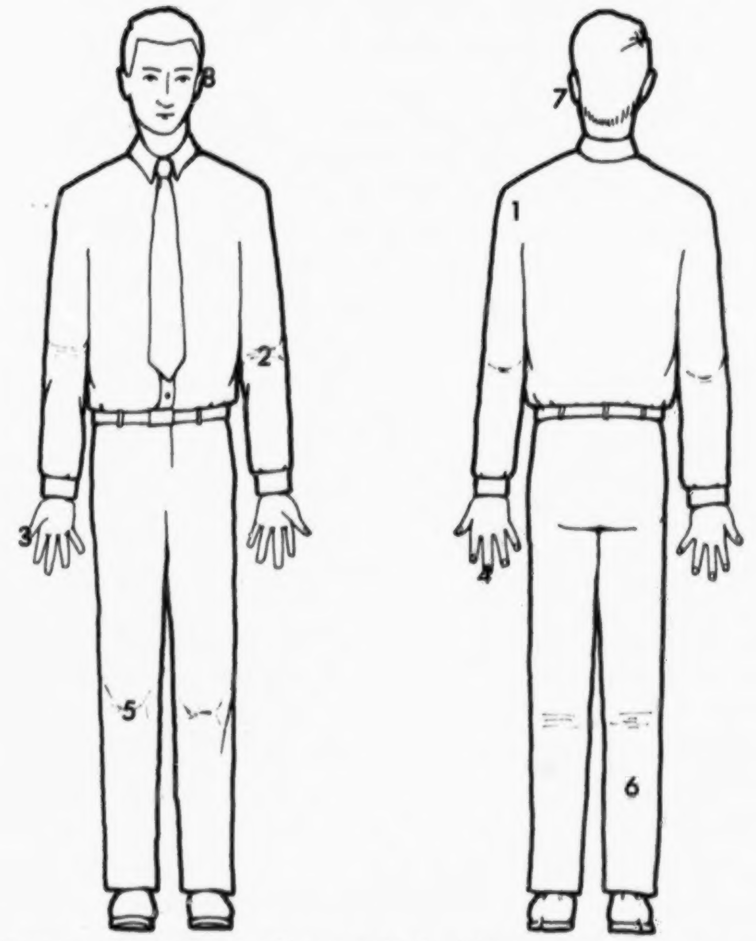


FIGURE 2.—Schema of human body on which different body parts are numbered. Facing this diagram (one of a series of five), the patient has to indicate, on his own body, each part designated on the diagram (based on Semmes, Weinstein, Ghent and Teuber, 1963, and modified by Corkin, unpublished).

used a multiple-choice procedure for the detection of concealed patterns, and by Green and his colleagues (1959) and, more recently, by Reed (1969) who employed a computer display in which the child has to detect the presence of vertical or horizontal striations in a visual noise.

All of these results fit the tentative generalization that early lesions may be less disruptive of certain elementary sensory or sensorimotor tasks than later lesions in man, but that a different picture emerges if we use tasks of another order of complexity: given the appropriate tasks, early lesions may then turn out to be just as disabling as later lesions, or even more so.

CROSSMODAL DEFICITS: A FALSE LEAD

The claim that early lesions produce grave defects of a sort previously missed or misinterpreted has also been advanced on other grounds. It is currently fashionable, in some quarters, to attribute much of the intellectual handicap following early brain injury in children to a very specific breakdown in what has been called "crossmodal" or "intersensory" learning. This claim is ill-founded and, probably, false.

Experiments on crossmodal matching typically involve the following: One presents to a child an array of tridimensional solids of different shapes that can either be compared by sight or by palpation (i.e., "haptically"). For example, five different shapes can be employed (Rudel and Teuber, 1964). The child is permitted to look at one of them, and this solid is then returned to a stand behind a black curtain, and the child has to find this solid by palpation among the others. Such a task would require crossmodal matching, from the visual to the haptic mode; the converse procedure (i.e., haptic-to-visual) would be to expose one solid to the child by letting him palpate it, and then asking him to find it again by looking for it among the others in the array. Such crossmodal tasks are quite difficult for young children, and particularly difficult for children with early brain damage, but this does not mean that early damage affects crossmodal matching selectively.

What is needed, of course, are corresponding tests of a child's capacity for solving such problems entirely within a particular modality, i.e., visual-to-visual, or haptic-to-haptic. When this is done (Rudel and Teuber, 1964), normal children do quite well on the visual-to-visual task, and rather poorly on the haptic-to-haptic. The crossmodal tasks (visual-to-haptic and haptic-to-visual) are of a difficulty intermediate between the easier unimodal task (visual-to-visual) and the more difficult one (haptic-to-haptic). In children with early brain damage, the performance differs from that of normal controls primarily by a marked reduction in the efficiency with which the unimodal, visual-to-visual tasks are done (Rudel and Teuber, 1969b). Thus, the level of achievement falls most markedly in that portion of the test series in which the normal children did best, with the result that there is a general leveling of performance across the tasks, without any differential drop in the crossmodal portions of the series. Previous claims for specifically crossmodal deficits were based on experiments in which the obvious control conditions (tests for efficiency of matching within a single modality) had been omitted.

Need for Intensive Analysis of Performance

We have stressed these seemingly fine points only to indicate once again how much depends on continued and systematic analysis of performance, before we can say what the nature of the behavioral deficits might be that follow early cerebral trauma in animal or man. And we would argue for the logical priority of these behavioral analyses, because unless we know at least dimly what it is that we are trying to localize, we cannot make much sense of our neuropathologic data.

Ultimately, neuropathology will have to decide between the two alternative interpretations of the apparent contrast between early and late lesions in man: One view holds that the lesions in the contrasting groups are simply not comparable, and that if similar lesions would exist in adults the effects would not be so different from those seen in children. The other more radical view implies that the contrasting behavioral consequences of early and late lesions reflect a corresponding contrast of cerebral organization between young and mature brains. Logically, the two alternatives are distinct, but in reality, both factors, a difference in lesion sites, and a genuine difference in the consequences of identical lesions, may contribute jointly to the kind of results we have encountered so far.

There are hints in our studies that point at a possible difference in the depth of the effective early lesions, as compared with the late-acquired ones. In the 63 children we are currently following, 50 have definite abnormalities of their oculomotor system. In the least severe instances, such abnormalities were restricted to an incoordination between hand and eyes so that the head rather than the eyes preceded on turning to a peripheral visual or auditory target. Perhaps the effective early lesions (i.e., those most readily detected and studied because of manifest neurologic and psychologic consequences) are those in which the midbrain is involved? Here again, we have a question rather than an answer. And which of these objective neurologic signs are preferentially associated with more general intellectual deficits? Very few investigators have even begun to look at these problems in this way, but we believe one should.

Suggestions for Reconciling the Seeming Divergence of Results Obtained from Animal and Man

Why are the pictures obtained after early lesions in animal and in man so disparate? On this problem, I believe the answer will come in time, and in two parts. So far, neither the cerebral lesions nor the tasks employed have been sufficiently comparable. We must make larger and deeper lesions, or, perhaps, combined cortical lesions and subcortical lesions in the very young animal brain before we can duplicate those lesions in man that might carry the gravest clinical risks. At the same time, we must look in the animal laboratory for certain tasks analogous to those that are so sensitive to early lesions in man.

Thus, we must make efforts to devise tests for animals that would correspond to those tasks for man that uncover non-specific deficits after early lesions, such as the hidden-figure tests and their variants. Moreover, we should be alert to test situations that might bring out odd results in animals, such as an abnormal increase (rather than the expected decrease) of sensitivity, analogous to the surprising hyperesthesia we have found in some children with early cerebral lesions. At the same time, we must pursue the almost unending task of searching for clinico-pathologic correlations in children with early lesions who succumb to some unrelated disease.

When all this is done, and it is a rather tall order, we may find that the results for animals and for man are no longer as incongruent as they seemed until now. It may turn out that in animals as in man, the early lesions are more likely to spare certain elementary functions until the lesion exceeds a critical size and depth, and that a variety of more complex aspects of performance are equally vulnerable in the young and in the mature brain, and in some respects even more vulnerable in the young.

Possible Mechanisms

Assuming that a difference in cerebral organization plays a role in the difference in outcome between early and late lesions, how can we account for it? We could assume that the young brain might possess a certain number of uncommitted neuronal elements, (Penfield, 1966) in addition to those innately specified neurons that act as feature detectors in the different sensory modalities (Hubel and Wiesel, 1959, 1965; Teuber, 1966). One might assume further that these uncommitted neurons become increasingly specified in the course of normal development to mediate higher-order abstractions within and beyond the particular sensory inputs. In the presence of massive lesions inflicted early on the very young brain, surviving uncommitted neurons would be recruited to participate in more elementary feature detection, rather than in higher order processing of sensory information.

The interpretation just offered is completely speculative but not impossible to test by appropriate microelectrode studies. Somewhat similar views have been expressed by Luria (1966) who credits them to his teacher Vygotskii (1960). Thus, Luria asserts (1966) that "disturbance of the relatively elementary processes of sensory analysis and interpretation will be decisively important in early childhood, for it will cause underdevelopment of all the formations for which it serves as a foundation. Conversely, the disturbance of these forms of direct sensory analysis and integration in the adult, in whom the higher functional systems have already formed, may have a more limited effect, compensated for by other differentiated systems of connections" (Luria, 1966, p.37).

The corresponding formulation by Vygotskii (1960), as summarized by Luria (in the literal rather than idiomatic English of the 1966 version of Luria's volume) is quite similar: "In the early stages of ontogeneis, a lesion of a particular area of the cerebral cortex will predominantly affect a higher (i.e., developmentally dependent on it) center than that where the lesion is situated; whereas in the stage of fully formed functional systems, a lesion of the same area of the cortex will predominantly affect a lower center (i.e., regulated by it)" (quoted from Luria, 1966, p.37).

Undoubtedly, these important conjectures have to be tested further. The relative importance of cortical and subcortical lesions is still unclear, and there are notorious difficulties in deciding which cerebral systems are "higher," and which ones "lower," in respect to perceptual and perceptual-motor functions and their development. It remains true, however, on a purely descriptive level, that the more elementary sensory functions seem less affected after early lesions, in our cases, than those more complex tasks that involve the discrimination and identification of patterns; and the converse seems to be true for the effects of later lesions where elementary functions appear to be more vulnerable than those involving higher-order classification of objects and events.

Only protracted study of these behavioral differences, followed by neuropathologic reconstruction of the cerebral lesions in large numbers of cases, can get us beyond the present, utterly unsatisfactory state of this field. It is plain that there is much more work in front of us than lies behind, in spite of the joint efforts in the laboratory and in the clinic. It is my conviction—but this is an act of faith—that future progress may be more rapid. It will accelerate, I am sure, if we continue to attack our problems jointly; that is, we must not permit the historical separation of neurology and psychology to endure, since it is only by their coalescence that we can deal with the problem of mind and brain, and with the mental deficiencies induced by early or later cerebral trauma.

REFERENCES

AKERT, A. K., et al. Learned behavior of rhesus monkeys following neonatal bilateral prefrontal lobotomy. *Science 132:* 1944–45, Dec. 30, 1960.

ALTMAN, J., and DAS, G. D. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats *J. Comp. Neurol. 124:* 319–335, June 1965.

ANGEVINE, J. B., Jr. Time of neuron origin in the hippocampal region; an autoradiographic study in the mouse. *Exp. Neurol. Suppl. 2:* 1–70, Oct. 1965.

BATTIG, K., ROSVOLD, H. E., and MISHKIN, M. Comparison of the effects of frontal and caudate lesions on delayed response and alternation in monkeys. *J. Comp. Physiol. Psychol. 53:* 400–404, Aug. 1960.

BENJAMIN, R. M., and THOMPSON, R. F. Differential effects of cortical lesions in infant and adult cats on roughness discrimination. *Exp. Neurol. 1:* 305–321, Oct. 1959.

BLACK, P. Post-traumatic syndrome in children. In: *The Late Effects of Head Injury.* A. E. Walker, C. MacDonald, and W. F. Caveness (eds.), Charles C Thomas 1969, pp. 142–149.

BLUM, J. S., CHOW, K. L., and PRIBRAM, K. H. A behavioral analysis of the organization of the parieto-temporo-preoccipital cortex. *J. Comp. Neurol. 93:* 53–100, Aug. 1950.

COBRINIK, L. The performance of brain-injured children on hidden-figure tasks. *Amer. J. Psychol. 72:* 566–571, Dec. 1959.

DAVIS, G. D. Caudate lesions and spontaneous locomotion in the monkey. *Neurology 8:* 135–139, Feb. 1958.

DIAMOND, I. T. The sensory neocortex. *Contrib. Sens. Physiol. 2:* 51–100, 1967.

DIAMOND, I. T., and NEFF, W. D. Ablation of temporal cortex and discrimination of auditory patterns. *J. Neurophysiol. 20:* 300–315, May 1957.

DOTY, R. W. Functional significance of the topographic aspect of the retino-cortical projection. In: *Neurophysiologie und Psychophysik des visuellen Systems.* R. Jung and H. Kornhuber (eds.), Springer, Berlin, 1961, pp. 228–245.

DOUGLAS, R. J. The hippocampus and behavior. *Psychol. Bull. 67:* 416–442, June 1967.

DUBOIS-REYMOND, E. *Uber die Grenzen des Naturerkennens.* Veit u. Co., Leipzig, 1872.

ETTLINGER, G. Preliminary observations reported at the International Neuropsychological Colloquium in Taormina, Sicily, September 1968.

GAZZANIGA, M. Paper presented at the International Neuropsychology Colloquim, Sicily, September 1968.

GOTTSCHALDT, K. Uber den Einfluss der Erfahrung auf die Wahrnehumung von Figuren. *Psychol. Forsch. 8:* 261–317, 1926.

GOTTSCHALDT, K. Uber den Einfluss der Erfahrung auf die Wahrnehumung von Figueren. II. Vergleichende Untersuchingen Uber die Wirkung figuraler Einprägung und den Einfluss spezifischer Geschehensverläufe auf die Auffassung optischer Komplexe. *Psychol. Forsch. 12:* 1–87, 1929.

GREEN, B. F., WOLF, A. K., and WHITE, B. W. The detection of statistically defined patterns in a matrix of dots. *Amer. J. Psychol. 72:* 503–520, Dec. 1959.

HABER, W. B. Effects of loss of limb on sensory functions. *J. Psychol. 40:* 115–123, 1955.

HALL, W. C., and DIAMOND, I. T. Organization and function of the visual cortex in hedgehog. I. Cortical cytoarchitecture and thalamic retrograde degeneration. *Brain Behav. Evol. 1:* 181–214, 1968.

HALL, W. C., and DIAMOND, I. T. Organization and function of the visual cortex in hedgehog. II. An ablation study of pattern discrimination. *Brain Behav. Evol. 1:* 215–243, 1968.

HARLOW, H. F. The development of learning in the rhesus monkey. *Amer. Sci. 47:* 459–479, Dec. 1959.

HARLOW, H. F., AKERT, K., and SCHILTZ, K. A. The effects of bilateral prefrontal lesions on learned behavior of neonatal, infant and preadolescent monkeys. In: *The Frontal Granular Cortex and Behavior,* J. M. Warren and K. Akert (eds.), McGraw-Hill, New York, 1964, pp. 126–148.

HARLOW, H. F., BLOMQUIST, A. J., THOMPSON, C. I., SCHILTZ, K. A., and HARLOW, M. K. Effects of induction age and size of frontal lobe lesions on learning in rhesus monkeys. In: *The Neuropsychology of Development,* R. L. Isaacson (ed.), Wiley, New York, 1968, pp. 79–120.

Hebb, D. O. The effect of early and late brain injury upon test scores, and the nature of normal adult intelligence. *Proc. Amer. Phil. Soc. 85:* 275–292, 1942.

Hebb, D. O. *The Organization of Behavior—a neuropsychological theory*. Wiley, New York, 1949.

Hubel, D. H. Single unit activity in lateral geniculate body and optic tract of unrestrained cats. *J. Physiol. 150:* 91–104, Jan. 1960.

Hubel, D. H., and **Wiesel**, T. N. Receptive fields of single neurons in the cat's striate cortex. *J. Physiol. 148:* 574–591, Oct. 1959.

Humphrey, N. K., and **Weiskrantz**, L. Vision in monkeys after removal of the striate cortex. *Nature 215:* 595–597, Aug. 5, 1967.

Isaacson, R. L., **Nonneman**, A. J., and **Schmaltz**, L. W. Behavioral and anatomical sequelae of damage to the infant limbic system. In: *The Neuropsychology of Development*. R. L. Isaacson (ed.) Wiley, New York, 1968, pp. 41–78.

Jacobsen, C. F. Functions of frontal association area in primates. *Arch. Neurol. Psychiat. 33:* 558–569, 1935.

Jeeves, M. A. Psychological studies of three cases of congenital agenesis of the corpus callosum. In: *Functions of the Corpus Callosum*. E. G. Ettlinger (ed.), Little, Brown and Co., Boston, 1965, pp. 73–94.

Kennard, M. A. Age and other factors in motor recovery from precentral lesions in monkeys. *Amer. J. Physiol. 115:* 138–146, March 1936.

Kennard, M. A. Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *J. Neurophysiol. 1:* 477–496, Nov. 1938.

Kennard, M. A. Cortical reorganization of motor function: Studies on series of monkeys of various ages from infancy to maturity. *Arch. Neurol. Psychiat. 48:* 227–240, Aug. 1942.

Kling, A. Amygdalectomy in the kitten. *Science 137:* 429–30, Aug. 10, 1962.

Kling, A., and **Tucker**, T. J. Effects of combined lesions of frontal granular cortex and caudate nucleus in the neonatal monkey. *Brain Res. 6:* 428–439, Nov. 1967.

Kling, A., and **Tucker**, T .J. Sparing of function following localized brain lesions in neonatal monkeys. In: *The Neuropsychology of Development*. R. L. Isaacson (ed.), Wiley, New York, 1968, pp. 121–145.

Klüver, H., and **Bucy**, P. C. Preliminary analysis of functions of the temporal lobes in monkeys. *Arch. Neurol. Psychiat. 42:* 979–1000, Dec. 1939.

Luria, A. R. *Higher Cortical Functions in Man*. Basic Books, New York, 1966.

Milner, B. Amnesia following operation on the temporal lobes. In: *Amnesia*. C. W. M. Whitty and O. L. Zangwill (eds.), Butterworths, London, 1966, pp. 106–133.

Milner, B. Paper presented at the International Neuropsychology Colloquium in Taormina, Sicily, September 1968.

Milner, B., and **Teuber**, H. Alteration of perception and memory in man: reflections on methods. Chapter in: *Analysis of Behavioral Change*. L. Weiskrantz (ed.), Harper & Rowe, New York, 1968, pp. 268–375.

Mishkin, M. Visual discrimination performance following partial ablations of the temporal lobe: II. Ventral surface *vs.* hippocampus. *J. Comp. Physiol. Psychol. 47:* 187–193, June 1954.

Mishkin, M., and **Pribram**, K. H. Visual discrimination performance following partial ablations of the temporal lobe. I. Ventral *vs.* lateral. *J. Comp. Physiol. Psychol. 47:* 14–20, Feb. 1954.

Penfield, W., and **Roberts**, L. *Speech and Brain Mechanisms*. Princeton University Press, Princeton, N.J., 1959.

Penfield, W. Speech perception and the uncommitted cortex. Chapter 9 in: *Brain and Conscious Experience*. J. C. Eccles (ed.), Springer, New York, 1966, pp. 217–237.

Raisler, R. L., and **Harlow**, H. F. Learned behavior following lesions of posterior association cortex in infant, immature, and preadolescent monkeys. *J. Comp. Physiol. Psychol. 60:* 167–174, Oct. 1965.

Reed, C. F. The solution of hidden figures: Brightness discrimination and eye movement. *Neuropsychologia,* 1969.

Riopelle, A. J., **Harlow**, H. F., **Settlage**, P. H., and **Ades**, H. W. Performance of normal and operated monkeys on visual learning tests. *J. Comp. Physiol. Psychol. 44:* 283–289, June 1951.

Rosvold, H. E., and Delgado, J. M. R. The effect on the behavior of monkeys of electrically stimulating or destroying small areas within the frontal lobes. *Amer. Psychol. 8:* 425–426, Aug. 1953.

Rudel, R. G., and Teuber, H. Crossmodal transfer of shape discrimination by children. *Neuropsychologia 2:* 1–8, June 1964.

Rudel, R. G., and Teuber, H. Spatial orientation in normal children and in children with early brain injury. *Neuropsychologia,* 1969.

Rudel, R. G., and Teuber, H. Pattern recognition within and across sensory modalities in normal and brain-injured children. *Neuropsychologia,* 1969.

Rudel, R. G., Teuber, H., and Twitchell, T. E. A note on hyperesthesia in children with early brain damage. *Neuropsychologia 4:* 351–356, Dec. 1966.

Russell, W. R. *Brain, Memory, Learning: A Neurologist's View.* Clarendon Press, Oxford, 1959.

Schneider, G. E. Contrasting visuomotor functions of tectum and cortex in the golden hamster. *Psychol. Forsch. 31:* 52–62, 1967.

Schneider, G. E. Retinal projections characterized by differential rate of degeneration revealed by silver impregnation. *Anat. Rec. 160:* 423, Feb. 1968.

Schneider, G. E. Two visual systems: Brain mechanisms for localization and discrimination are dissociated by tectal and cortical lesions. *Science 163:* 895–902, 1969.

Schneider, G. E., and Nauta, W. J. H. Formation of anomalous retinal projections after removal of the optic tectum in the neonate hamster. *Anat. Rec.* 1969.

Semmes, J., et al. Spatial orientation in man after cerebral injury. I. Analyses by locus of lesion. *J. Psychol. 39:* 227–244, 1955.

Semmes, J., et al. *Somatosensory Changes After Penetrating Brain Wounds in Man.* Harvard Univ. Press, Cambridge, Mass., 1960.

Semmes, J., et al. Correlates of impaired orientation in personal and extrapersonal space. *Brain 86*: 747–772, Dec. 1963.

Sharlock, D. P., Tucker, T. J., and Strominger, N. L. Auditory discrimination by the cat after neonatal ablation of temporal cortex. *Science 141:* 1197–1198, Sept. 20, 1963.

Sperry, R. W. Hemispheric interaction and the mind-brain problem. In: *Brain and Conscious Experience.* J. D. Eccles (ed.), Springer, New York, 1966.

Strich, S. The pathology of brain damage due to blunt head injuries. In: *The Late Effects of Head Injury.* A. E. Walker and W. F. Caveness (eds.), Charles C. Thomas, Springfield, Ill. 1969, pp. 501–526.

Teuber, H. Physiological psychology. *Ann. Rev. Psychol. 6:* 267–296, 1955.

Teuber, H. Some alterations in behavior after cerebral lesions in man. In: *Evolution of Nervous Control from Primitive Organisms to Man.* Washington, D.C., Amer. Assoc. Adv. Sci., 1959, pp. 157–194.

Teuber, H. Alterations of perception after brain injury. Chapter 8 in: *Brain and Conscious Experience.* J. C. Eccles (ed.), Springer, New York, 1966, pp. 182–216.

Teuber, H., Krieger, H. P., and Bender, M. B. Reorganization of sensory function in amputation stumps: Two-point discrimination. *Fed. Proc., Fed. Amer. Socs. Exp. Biol. 8:* 156, 1949.

Teuber, H., and Liebert, R. S. Specific and general effects of brain injury in man: Evidence of both from a single task. *Arch. Neurol. Psychiat. 80:* 403–407, Oct. 1958.

Teuber, H., and Proctor, F. Some effects of basal ganglia lesions in subhuman primates and man. *Neuropsychologia 2:* 85–93, Oct. 1964.

Teuber, H., and Rudel, R. G. Behavior after cerebral lesions in children and adults. *Develop. Med. Child Neurol. 4:* 3–20, Feb. 1962.

Teuber, H., and Weinstein, S. Ability to discover hidden figures after cerebral lesions. *Arch. Neurol. Psychiat. 76:* 369–379, Oct. 1956.

Tsang, Y. Maze learning in rats hemidecorticated in infancy. *J. Comp. Physiol. Psychol. 24:* 221–253, Oct. 1937.

Tsang, Y Visual sensitivity in rats deprived of visual cortex in infancy. *J. Comp. Physiol. Psychol. 24:* 255–262, Oct. 1937.

Tucker, T. J., and Kling, A. Differential effects of early *vs.* late brain damage on visual duration discrimination in cat. *Fed. Proc., Fed. Amer. Socs. Exp. Biol. 25:* 207, Mar.-April, 1966.

Tucker, T. J., and Kling, A. Differential effects of early and late lesions of frontal granular cortex in the monkey. *Brain Res. 5:* 377–389, July 1967.

TWITCHELL, T. E., et al. Minimal cerebral dysfunction in children: Motor deficits. *Trans. Amer. Neurol. Ass. 91:* 353–355, 1966.

VIGNOLO, L. A. Factors underlying impairment of visual figure-ground discrimination and sorting tasks in hemisphere-damaged patients. In: *Hemispheric Asymmetry of Function.* M. Kinsbourne (ed.), Tavistock, London, 1969.

VYGOTSKII, L. S. *Development of the Higher Mental Functions.* (In Russian) Izd. Akad. Ped. Nauk., RFSR, Moscow, 1960.

YAMAGUCHI, S., and MYERS, R. E. *Early versus late forebrain commissure section and interocular transfer of visual learning.* Paper read at Eastern Psychol. Assoc. Meeting, Philadelphia, Pa., April 12, 1969.

ZUBEK, J. P., FLYE, J., and AFTANAS, M. Cutaneous sensitivity after prolonged visual deprivation. *Science 144:* 1591–1593, June 26, 1964.

SESSION II

Epidemiology

Session Chairman: ROGER J. MEYER, M.D.

THE EPIDEMIOLOGY OF HEAD TRAUMA IN CHILDHOOD—INTRODUCTORY COMMENTS

ROGER J. MEYER, M.D., M.P.H.
Northwestern University
School of Medicine
Infant Welfare Society
Chicago, Illinois.

> "Humpty Dumpty sat on a wall,
> Humpty Dumpty had a great fall,
> All the king's horses and all
> the king's men
> Couldn't put Humpty Dumpty
> together again."
>
> *Mother Goose*

The epidemiologic complexity of head trauma in childhood is as difficult to put together into a cohesive, understandable whole as it is to restore the child with severe head injury to complete health. It is this understanding, however, which is most likely to lead to the control of the incidence and disability of this leading problem.

The rapidly changing developmental status of children at each age combines with the complexities of assessing the effect of injury upon this process to make the accurate study of head trauma in the young child a difficult process. The most reasonable estimates can only be accomplished by following a defined population for an extended period of time; alternative means of determining the extent of damage are subject to gross error. Epidemiology offers a systematic approach to defining and understanding the problem.

Study Methods for the Child with Postnatal Trauma

Excluding for the moment the steadily mounting factual data dealing with the perinatal period, it is worthwhile focusing upon the child who suffers trauma after this period. Two methods of study are available. The prospective analysis follows a defined population of children over a specific period of time, providing information about incidence, severity circumstances of injury, and its relationship to the individual's previous state. Few such studies exist because of their relative cost in terms of professional skills, time and money consumed by such research. They provide the most accurate measure of the problem for a unit population.

The retrospective study is far more common, usually investigating a population of hospitalized patients, school children or mortality sample. While selection introduces bias, it also provides information about those presumably at greatest risk from head injuries. The majority of the epidemiologic references deal with this type of study.

Existing information (see the bibliography appended) suggests that (1) individual susceptibility varies widely among children, (2) human adaptability following head trauma is greater than previously reported, and (3) a wide variety of sequelae must be considered in evaluating the results of trauma, including mental retardation, perceptual disorders, emotional and motor as well as seizure manifestations. Since few studies have more than negative history on children as evidence of normalcy preceding trauma, it is extremely difficult to assess even clear-cut clinical evidence of post-traumatic convulsions, mental retardation and other problems attributed to trauma. A brief review of the literature indicates that a variety of generally incomplete criteria are often used to define post-traumatic results without considering the role of these criteria as possible causes of the trauma (falls, child abuse, vehicular injury). The impulsive, aggressive, daredevil child may actually be quite different neurophysiologically from those often cited as "high-risk" who are not so frequently injured. Psychological appraisal of the brain-injured child is a continuing process which also becomes more precise as the child grows older. Severe physical and electroencephalographic changes may tend to disappear with the developmental process. Experimental work with many species indicates variation of post-injury results with type of animal, age, brain area, and extent of trauma.

Demographic Factors

The incidence of head trauma among children is influenced by a number of demographic factors. First, the child's family structure, social class, and parental history of injury are associated with susceptibility to injury. Children from less stable or one-parent families, lower income groups, or more hazardous homes are more likely to have both a higher incidence of head injuries and more severe injuries. So too are those with parents who have more frequent injuries themselves, who have more fatalistic attitudes about injuries, and who provide more casual supervisory arrangements for their children. Conversely, children with both parents living in the home, from families with higher social class and income, and greater concern and positive attitudes about child care have fewer children with head injuries, particularly from vehicular trauma and other injuries outside the home. This tendency increases with the child's age. Boys have several times greater incidence of head injuries, with a peak incidence for both sexes in the 3–6 year pre-school age group.

Patterns of Injury

The pattern of injury changes with falls from a dressing table, bed or other elevation while untended by an adult. This type of injury is found just as frequently in all social classes, but more commonly with young, inexperienced mothers under stress. The toddler and pre-school child is most frequently injured by falling from a height while either climbing or attempting to reach a less accessible area (window, counter). The pre-school and school-age child are more frequently injured either from climbing or vehicular impact as a pedestrian. Head injuries to child passengers of automobiles are not apparently altered by increased availability of seat belts, possibly due to limited use. Statistics for this and other types of head injuries are difficult to accumulate on a defined population.

The epidemiology of head injuries with particular reference to children is then demonstrated to be a tangled thicket of associations which vary with the age and sex of the individual, physiologic state, and human and physical surroundings. Increased mobility and exposure to hazards sharply increases male candidacy for head injury. It has been observed that more head injuries take place during the spring of the year, and that this relates to increased activity and exposure to hazards during that period as compared to other seasons. The pre-school child, with his intense driving activity and uncritical judgement, is at greatest risk, followed by the older person who is perhaps losing faculties and strength in a reversal of the same process experienced by the child. More head injuries seem to occur during the period of time between 3:00–6:00 P.M. for the young child, leading some investigators to consider fatigue and problems of adult supervision as combined factors increasing susceptibility during this period of the day.

Summary

In summary, the epidemiology of head injury is influenced by multiple, interlocking factors dealing with the characteristics of the injured person, the physical environment and—most important—the protective human environment, whether it be a supervising parent, fellow motorists, or interaction of a group. As further analysis of the clusters of variables is accomplished, preventive measures will also become evident. These may also be useful in reducing severity as well as incidence of head trauma.

TRAUMA AND MENTAL RETARDATION

NATHAN MALAMUD, M.D.
The Langley Porter Neuropsychiatric Institute
California Department of Mental Hygiene
San Francisco, California

The effects of perinatal and postnatal trauma will be considered separately, since it is well known that birth trauma is by far the more common and significant cause of mental retardation.

Perinatal Trauma

The designation of birth trauma in its broadest sense includes not only mechanical effects but also all manifestations of abnormal parturition associated with a great variety of circulatory and biochemical alterations. Following Little, who first drew attention to the problem over 100 years ago, it has become increasingly apparent that induced mechanical effects from obstetrical manipulation play a relatively minor role in the etiology of mental retardation and cerebral palsy.

But despite his pioneering work on asphyxia neonatorum, Little did not investigate its pathology, so that only one of 47 cases he reported in 1862 had an autopsy study, and this was restricted to gross observation. It was not until Schwartz undertook his many studies from 1923 to date, that a more comprehensive pathology of perinatal trauma began to take shape.

Recent studies, such as those by Gruenwald, Towbin, Clark and Anderson, and Banker and Larroche have confirmed many of Schwartz's pathoanatomic studies.

The chronic residual changes that concern us here have remained controversial. Thus, while some investigators maintain that certain lesions are characteristic and even pathognomonic of perinatal trauma sequelae, others reject this as unproved. Still others include a great number of conditions that appear to some to be totally unrelated.

From a review of the literature and this author's own material, three patterns of chronic lesions appear to be most closely linked with perinatal trauma, *viz.*, (1) sclerosis and/or cavitation of the cerebral white matter, (2) status marmoratus (marble state), and (3) sclerotic microgyria (ulegyria).

Sclerosis-cavitation of the white matter (fig. 1a) varies from a restricted paraventricular location in the walls of the lateral ventricles (Schwartz, Norman) to more extensive involvement of the centrum semiovale up to the cortex, either in the form of cystic degeneration (Benda) or diffuse sclerosis. In my experience the lesions are predominantly located in dorsal parts of the hemispheres and seldom involve the ventral regions. They are usually bilaterally symmetrical but at times are entirely unilateral (fig. 1b). The sclerotic changes are characterized microscopically by a dense gliosis (fig. 1c) that either undermines the cortex or extends irregularly into the deep layers in the form of local cell loss, (fig. 1d), thus forming a transition to the condition of sclerotic microgyria.

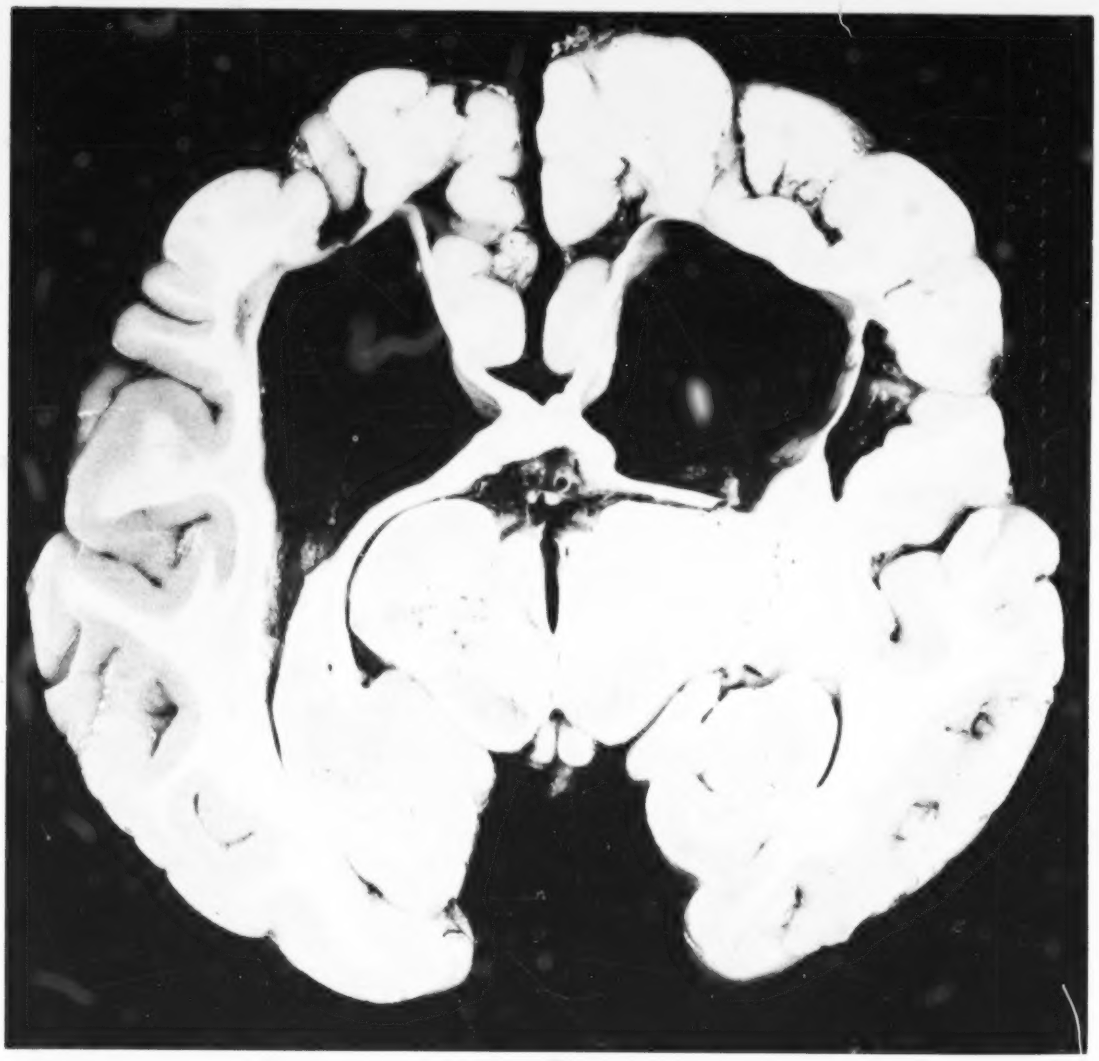


FIGURE 1.—(a) Coronal section, showing bilateral atrophy and cystic degeneration of white matter of parietal region, with corresponding dilatation of lateral ventricles; (b) coronal section, showing unilateral atrophy and cystic degeneration of frontal white matter, caudate nucleus and thalamus with local dilatation of lateral ventricles; (c) diffuse sclerosis and cavitation of white matter with slight penetration of cortex, Holzer glial fiber stain; (d) diffuse atrophy of gyral white matter and focal loss of neurons in deep layers of cortex, Nissl stain X 25.

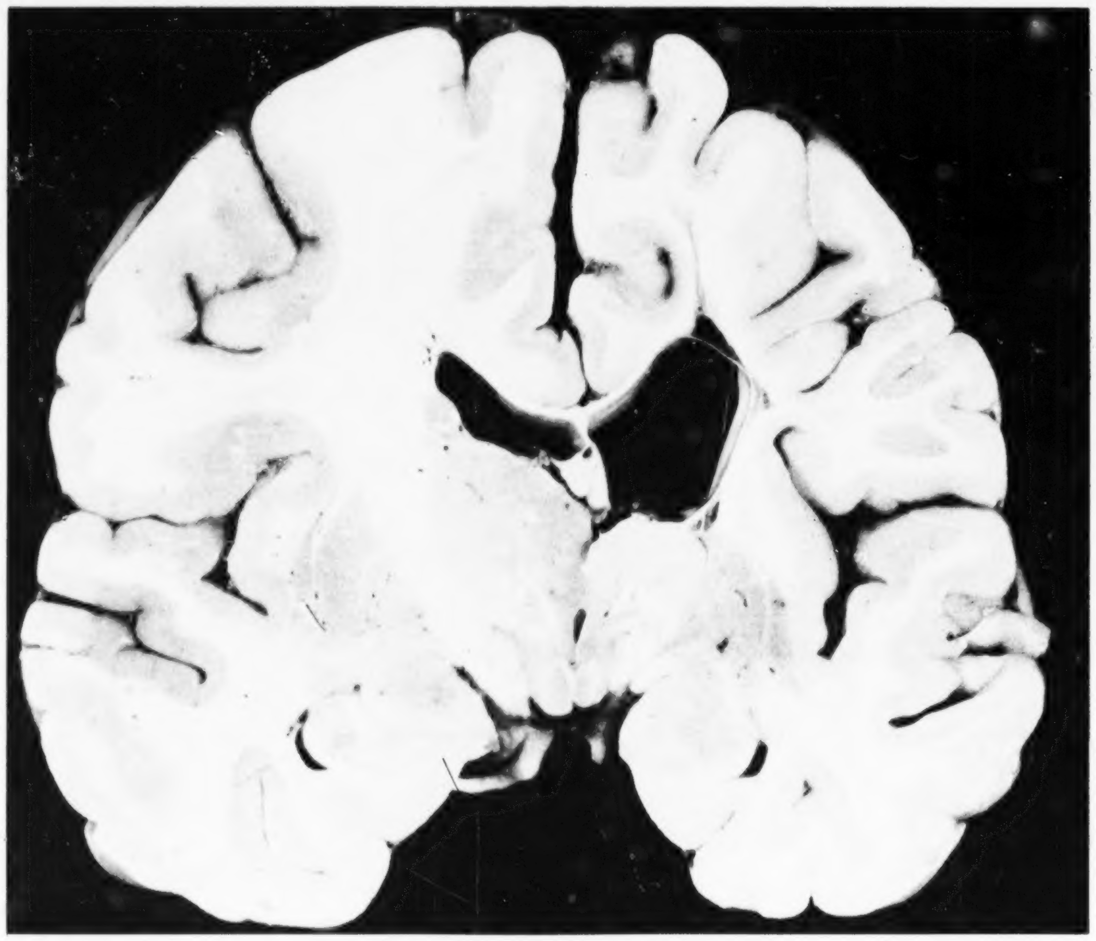


FIGURE 1–b.

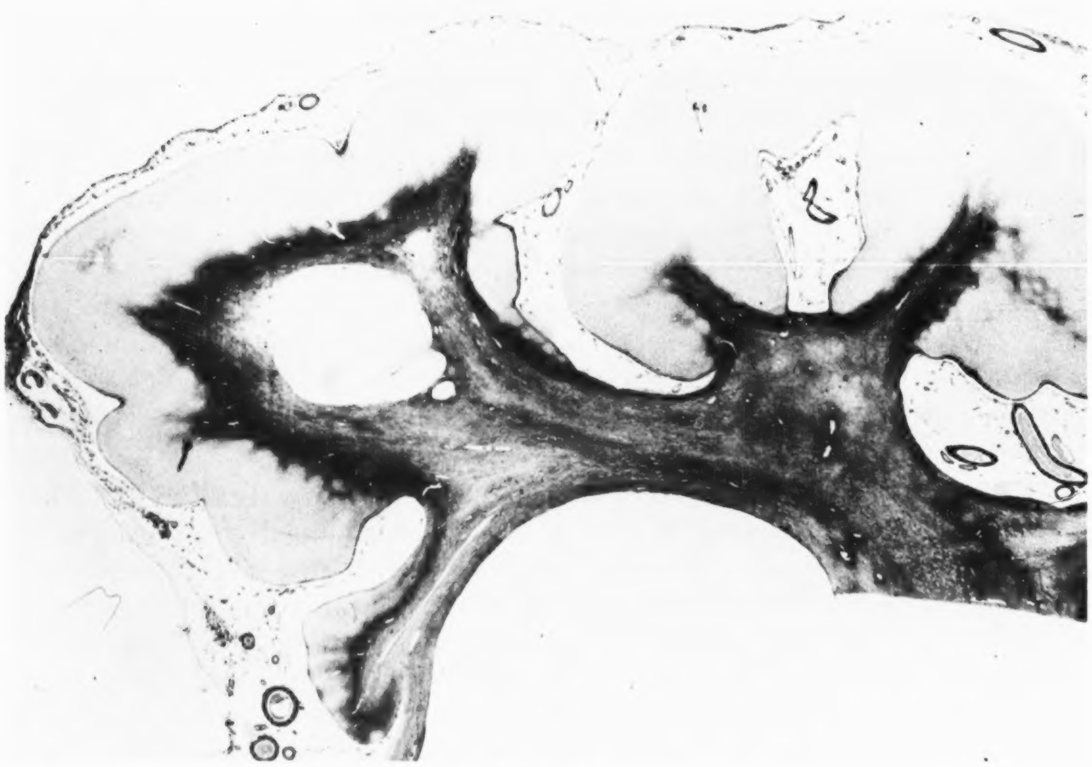


FIGURE 1–c.

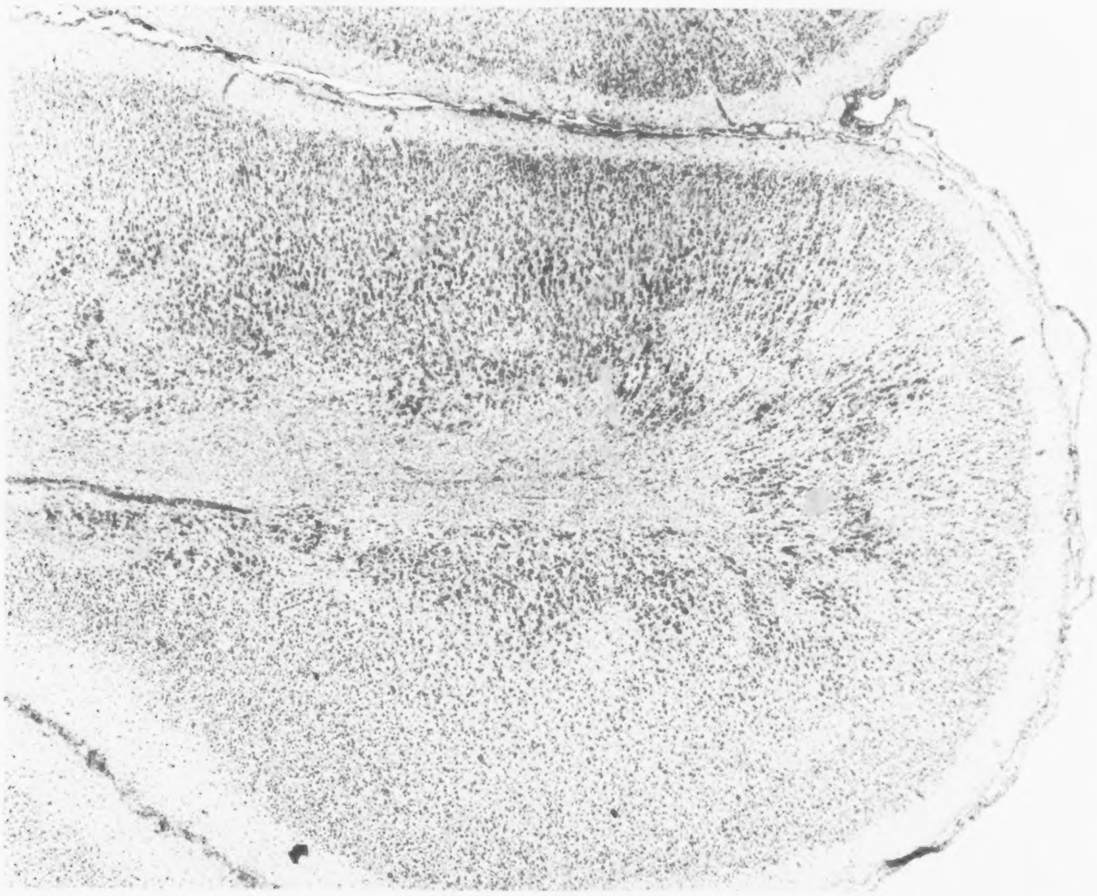


FIGURE 1–d.

Such lesions in the white matter are perhaps the most clearly related to disturbances in the deep Galenic venous system, especially those involving territories drained by the anterior terminal or lateral ventricular tributaries. They appear to correspond to the location of the periventricular hemorrhages and to the areas of leukomalacia noted in cases of neonatal death.

Status marmoratus (fig. 2a) has been described as a change in the basal ganglia, predominantly the putamen, caudate nucleus and thalamus, characterized by ramifying white fibers arranged in bundles or networks. In glial preparations the bundles consist of a network of dense glial fibers (figs. 2b, c, d); in myelin preparations they correspond to increased numbers of fine medullated fibers (fig. 2e); and in Nissl preparations they correspond to areas of abundant glial nuclei that are depleted of neurons, the few surviving cells often undergoing calcification (fig. 2f). This condition is subject to such variations as diffuse fibrosis or cyst formation.

First described by Anton, this disorder was initially considered by C. and O. Vogt and later by Alexander to be a genetically determined malformation. In more recent years a number of investigators have attributed it to birth trauma. The seemingly paradoxical feature of hypermyelination in a lesion that is fundamentally a form of neural degeneration with reactive gliosis is probably not of fundamental importance. While status marmoratus has at times been observed in other disorders, in my experience it has been one of the most constant sequelae of perinatal trauma: Like the changes in the white matter with which it is often combined, it also tends to occur in a bilaterally symmetrical and often dorsal lo-

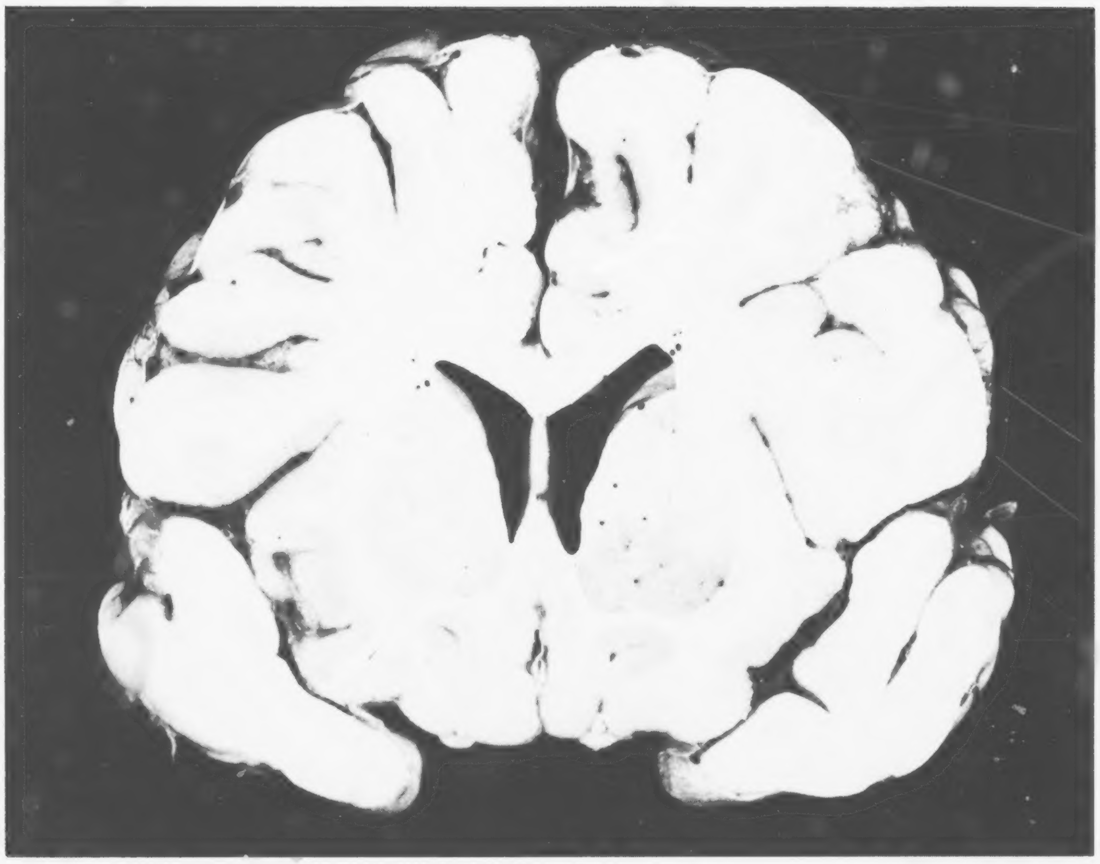


FIGURE 2.—(a) Coronal section, showing bilateral status marmoratus of corpus striatum; (b) status marmoratus in dorsal parts of corpus striatum with diffuse sclerosis of surrounding white matter, Holzer stain; (c) status marmoratus in medial nucleus and diffuse sclerosis of lateral nucleus of thalamus, Holzer stain: (d) status marmoratus of basal ganglia, characterized by focal gliosis, Holzer stain X 135; (e) same, showing hypermyelination in areas of gliosis, Woelcke's myelin stain X 100; (f) same, showing focal neuronal loss, adjacent to relatively preserved areas, Nissl stain X 160.

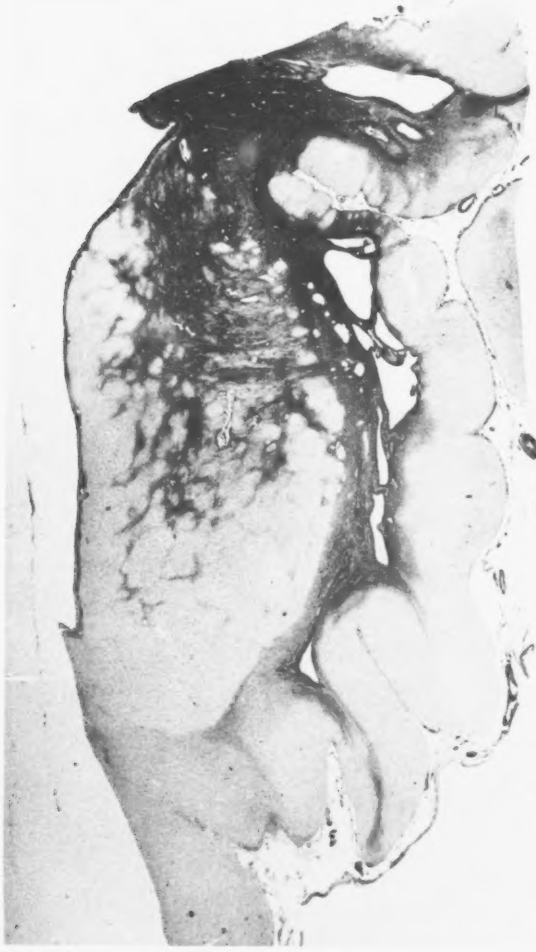


FIGURE 2–b.

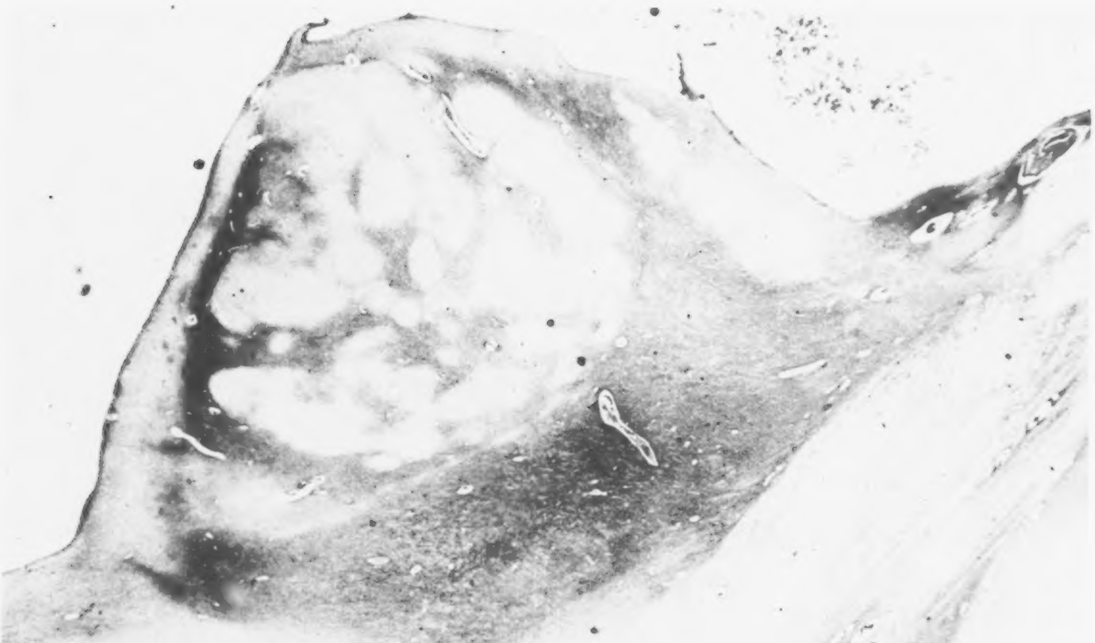


FIGURE 2–c

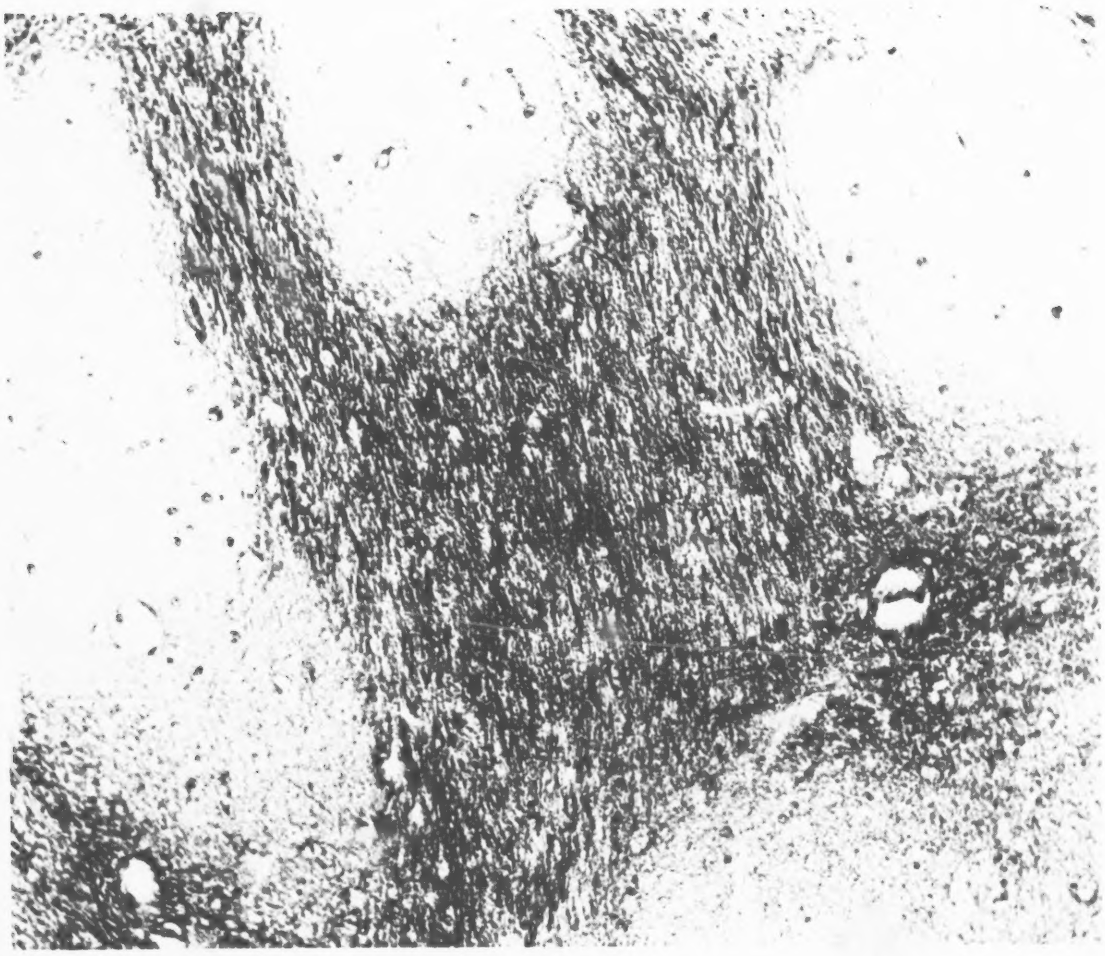


FIGURE 2–d.

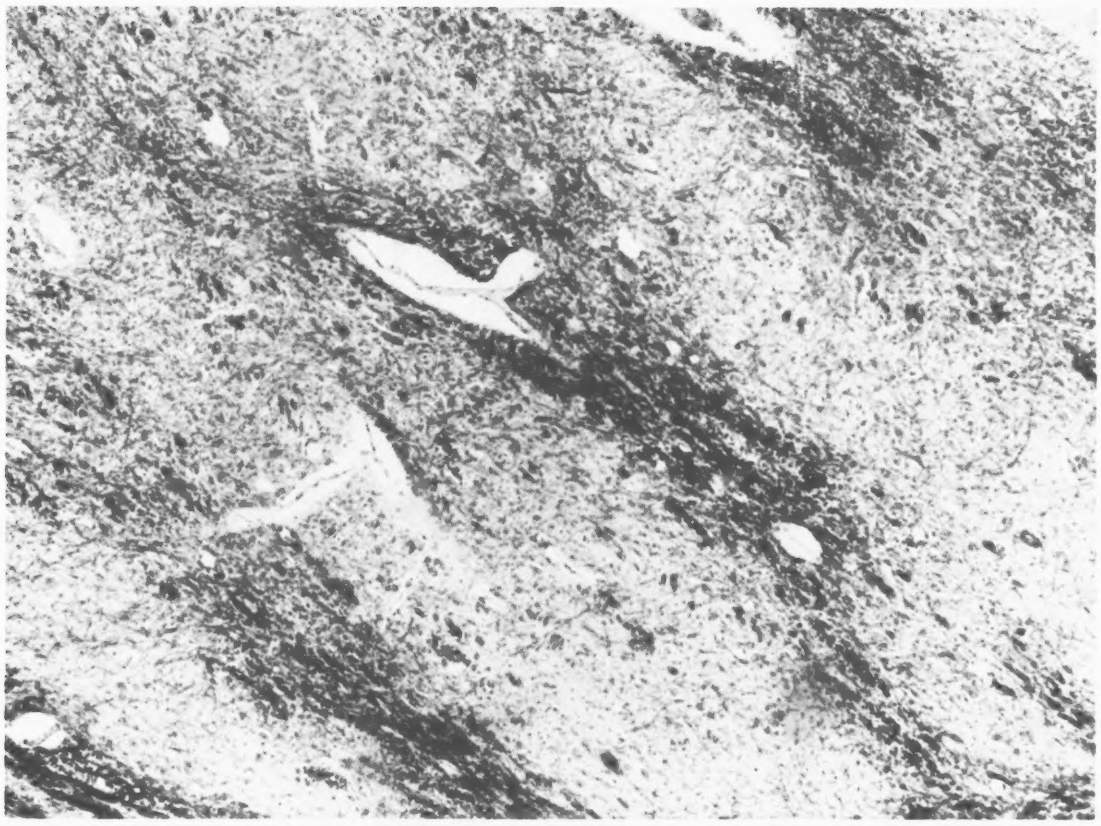


FIGURE 2–e.

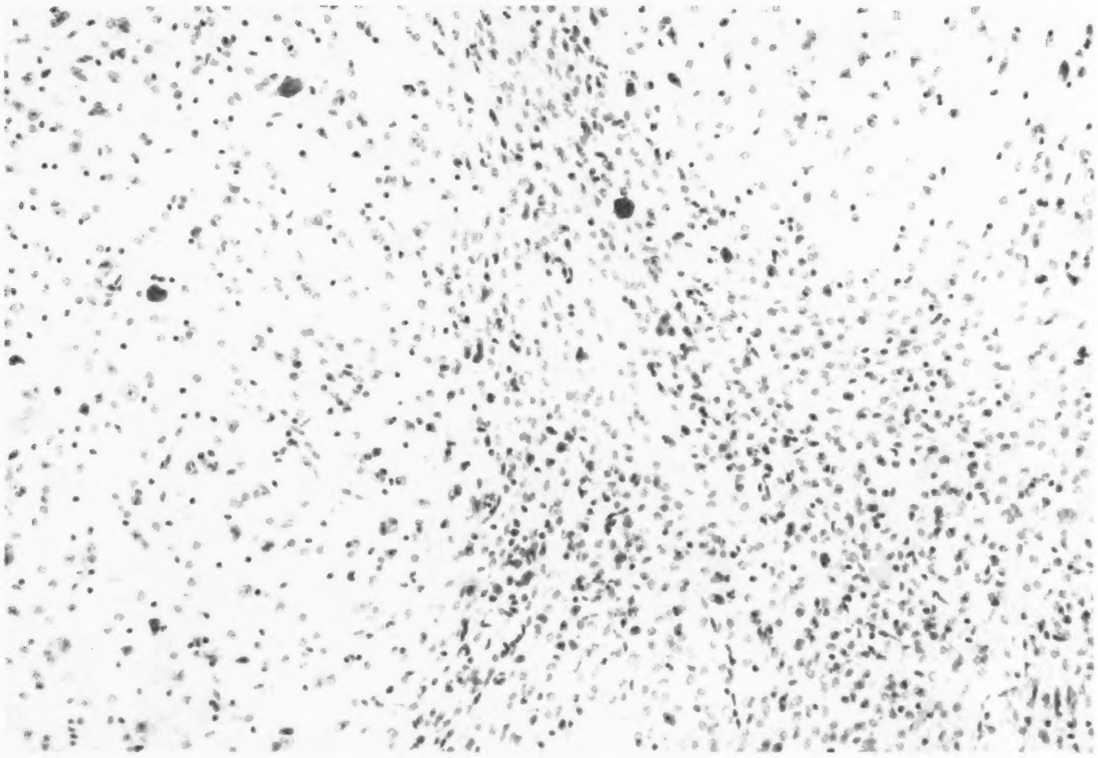


FIGURE 2–f.

cation. A comparison may be drawn between status marmoratus and the ischemic focal lesions in the basal ganglia of neonates reported by Clark and Anderson.

Sclerotic microgyria (fig. 3a) is characterized grossly by focal gyral atrophy yet associated with obliteration of sulci; the changes are most often found in bilaterally symmetrical dorsal parts of parieto-occipital, central, or anterior frontal regions. The basal cortex is usually spared (fig. 3b). Microscopically (fig. 3c), local sclerosis of white matter is associated with cortical gliosis involving primarily the walls of convolutions in the depths of sulci with relative sparing of the crowns of gyri, resulting in the characteristic gross appearance. Here, too, hypermyelination in the form of plaques fibromyeliniques with corresponding patterns of radial scars and status marmoratus are common (fig. 3d). The counterpart to ulegyria in acute stages of perinatal trauma has not been reported. Nevertheless, the common association of this lesion with the previously described changes in the white matter and basal ganglia, its anatomic location, and its tendency to a marbled pattern would argue for a close causal relationship among all three types of changes.

The question arises as to whether other patterns of lesions have been observed with any consistency under conditions of perinatal trauma. In his extensive studies of cerebral palsy, Courville included other types of cortical atrophy, demyelinating disorders, "status dysmyelinisatus," etc., in this category on the basis of his belief that a process of anoxia, comparable to that observed in adults, is the common underlying factor. He believed that all these conditions occurred at birth.

In previous studies I have attempted to distinguish between these different disorders on the basis of correlated clinical and pathologic data. Table 1 lists the neuropathologic findings in a series of cases over a 20-year period from California hospitals for the mentally retarded.

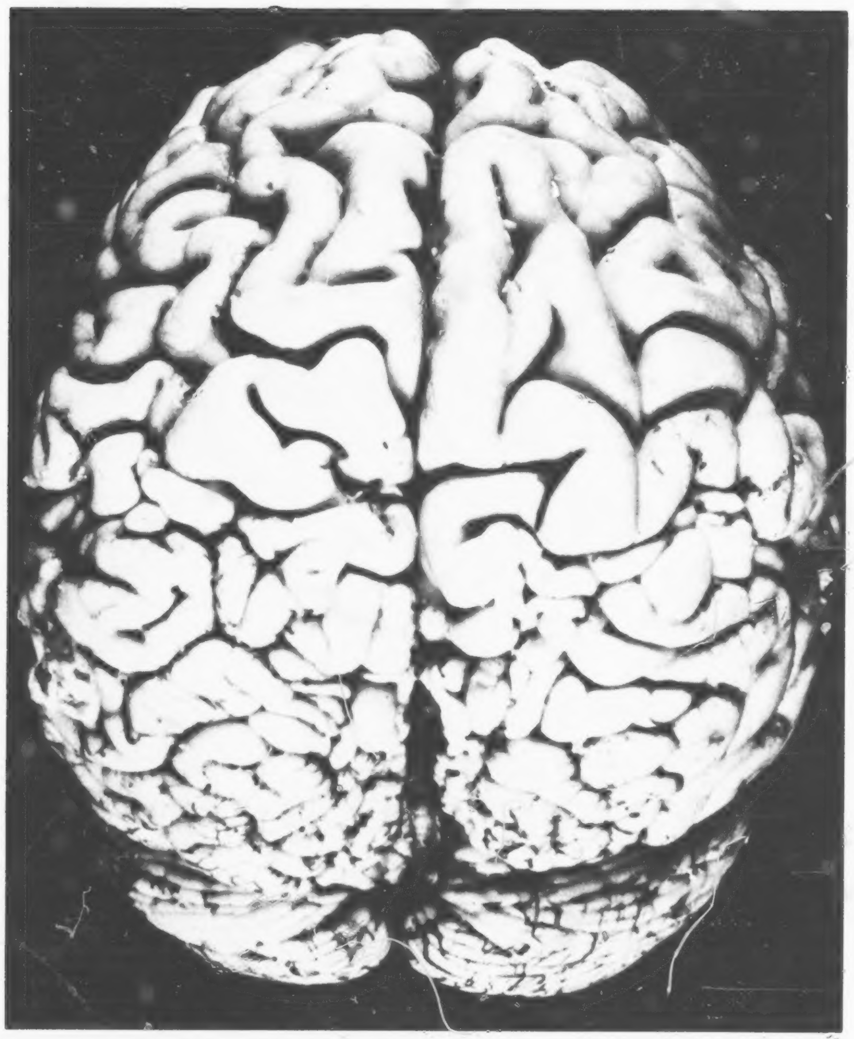


FIGURE 3.—(a) Dorsal view of cerebral hemispheres, showing bilateral sclerotic microgyria in parieto-occipital regions; (b) same in coronal section; (c) same, showing radial and marbled pattern of gliosis in cortex and diffuse sclerosis of white matter, Holzer stain; (d) same, with radial sclerosis alternating with preserved parts of cortex, Holzer stain X 75.

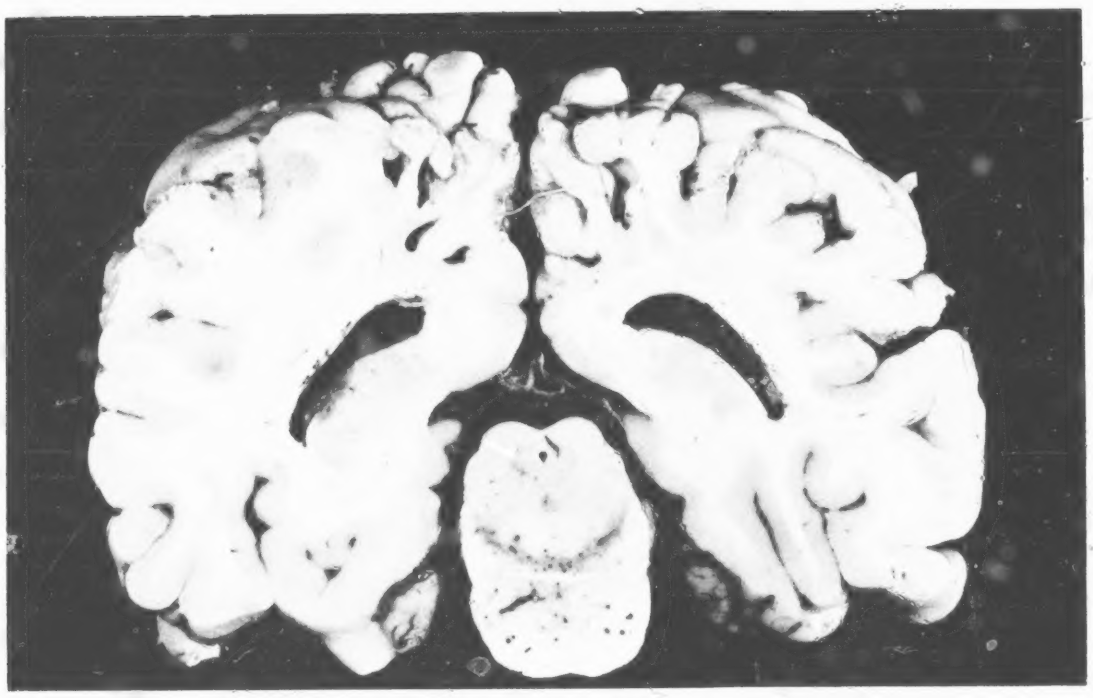


FIGURE 3–b.

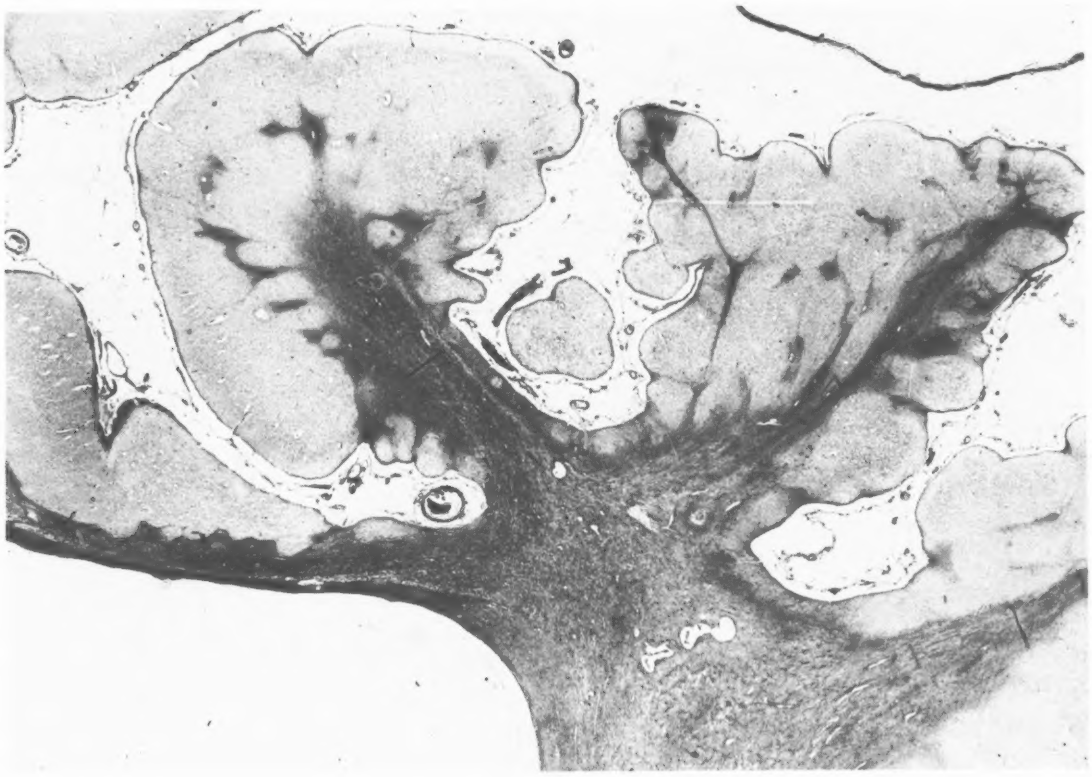


FIGURE 3–c.

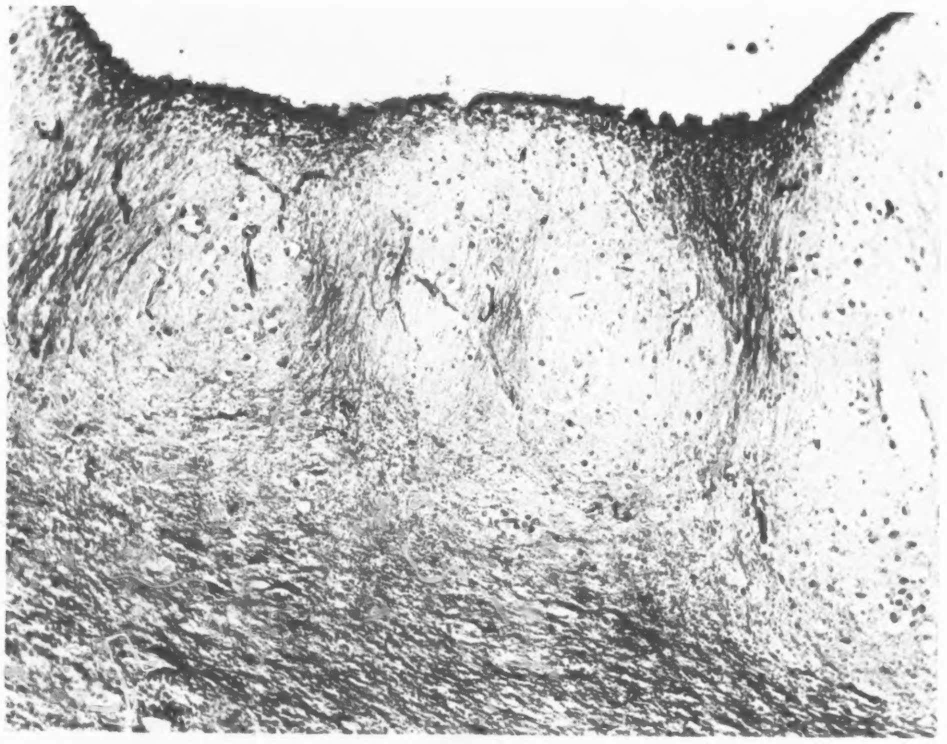


FIGURE 3–d.

TABLE 1.—*Classification of neuropathologic findings in mental retardation*

Type of Disorder			Number of Cases	Percent of Total
A. Developmental			1,590	67.5
1. Malformations	390			
2. Nonspecific arrested development	867			
3. Down's syndrome	333			
B. Destructive			598	25.4
1. Sequelae of perinatal trauma	248	(10.5%)		
2. Postinfectious	120			
3. Postepileptic	53			
4. Posticteric	35			
5. Sequelae of vascular occlusion	18			
6. Sequelae of postnatal trauma	8	(0.34%)		
7. Undetermined	116			
C. Metabolic			136	5.7
D. Proliferative			33	1.4
Total			2,357	100.0

Group B represents sequelae of nonprogressive destructive processes. It is here especially that clinicopathologic correlations in adequately investigated cases may be expected to establish specific patterns that could reflect the etiology of a given disorder. For example, the pathologic sequelae of kernicterus are sufficiently consistent to correlate with a history of icterus neonatorum. The same applies to sequelae of infectious disorders, although here more information is needed.

More controversial is the area of so-called postepileptic disorders in which fairly consistent histories of convulsions, with or without fever, occurring in infancy and childhood are elicited. Under such conditions, the cerebral changes may be characterized as those of anoxic encephalopathy resembling anoxic states of adults. This type of lesion has been most often confused with sequelae of perinatal trauma. A comparison between the two conditions is shown in figure 4, in which patterns of primarily subcortical pathology characteristic of birth trauma contrast with those of predominantly cortical pathology characteristic of the post-epileptic group.

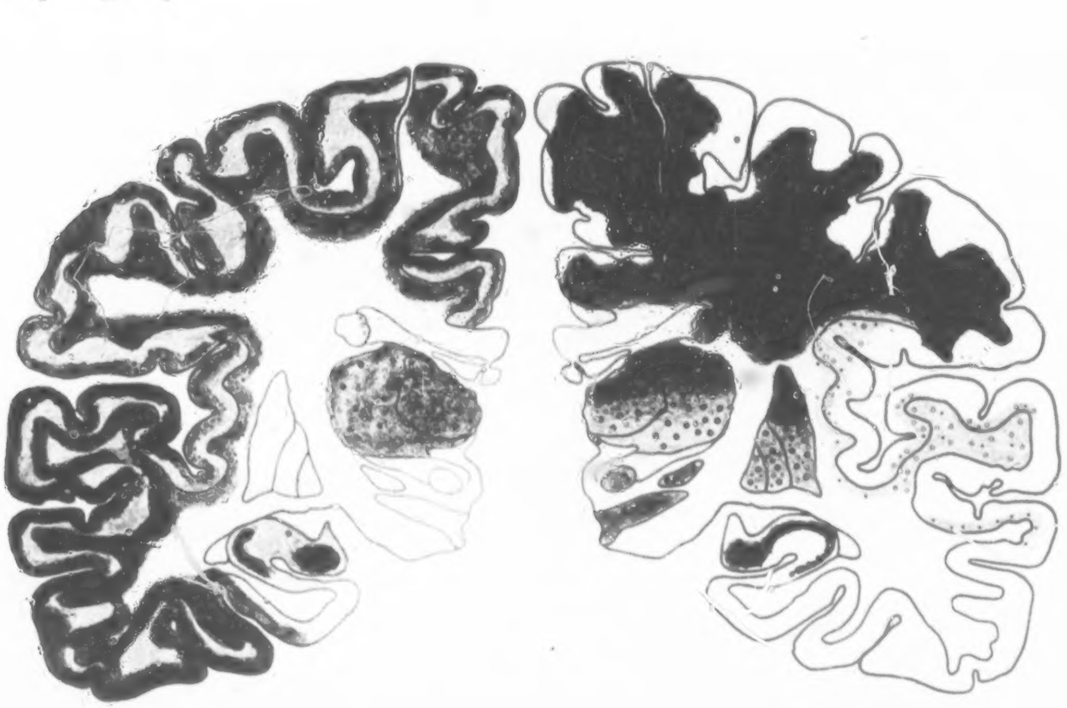


FIGURE 4.—Diagram illustrating distribution of lesions under conditions of perinatal trauma on right side contrasted with location of lesions in post-epileptic group.

About 10 percent in the series, 248 cases, were considered to have sequelae of perinatal trauma. Of these, 198 cases had a birth history that could be correlated with pathologic findings (Table 2).

TABLE 2.—*Historical data in 198 cases of presumed perinatal trauma*

	Number of Cases	Percent of Total
Abnormalities of labor and fetal abnormalities at birth	149	75
Normal labor and fetal abnormalities at birth	36	18
Normal labor and normal fetus at birth	13	7
Total	198	100

Among the most common abnormalities of labor and delivery were prolonged or difficult labor, 73 instances; instrumental or other manipulative delivery, 56; precipitous delivery, 22; multiple births, 14; abnormal presentation, 22 (of which 15 were breech); cesarean section, 12; placental abnormality, 11; cord abnormality, 15; and maternal illness, such as toxemia, 22. Several of these factors were often combined, but the extent to which each or any of these played a role in the resulting brain damage remains unknown. Prematurity was recorded in 30 percent, while 70 percent were full-term deliveries.

Probably of greater significance than the maternal difficulties was the high incidence of signs of fetal and neonatal distress. In the immediate postnatal period, respiratory difficulties were reported in 78 infants, resuscitation measures in 66, convulsions in 70, paralysis in 15, and head trauma in 20. Convulsions and swallowing and feeding difficulties were common throughout the neonatal period. Other clinical data of interest were sex and birth order: 57 percent were males and 43 percent were females; 50 percent were firstborn. The ages at death ranged from 6 weeks to 80 years. The main mental and neurologic sequelae were as follows:

TABLE 3.—*Clinical data in 198 cases of perinatal trauma*

Degree of Mental Retardation	Percent	Types of Neurologic Sequelae	Percent
Severe	83	Quadriplegia	56
Moderate	9	Hemiplegia	6
Mild	8	Athetosis	7
		Mixed states	21
		Epilepsy	81

The principal cerebral changes were:

TABLE 4.—*Pathoanatomic data in 198 cases*

Pattern of Lesions	Number of Cases	Percent of Total
Sclerosis-cavitation of cerebral white matter	164	83
Status marmoratus of striatum and/or thalamus	173	88
Sclerotic microgyria	132	62

One or another of the above three patterns of lesions was present in all but one case. Exclusive affection of the cerebral white matter was noted in 5, status marmoratus alone in 39, sclerotic microgyria alone in none; combinations of 2 or 3 patterns were observed in 153 cases. Involvement of other areas of the central nervous system was much less common, and when present was invariably associated with the above lesions. Of these, the globus pallidus was affected in 31, the mammillary body in 12, the subthalamic body in 11, the tectotegmentum of the midbrain or pons in 23, and the nucleus amygdala in 4 instances. In four cases there were also chronic subdural hematomas. In only one of the 198 cases was there an entirely different pattern, *viz.*, bilateral infarcts in a carotid arterial distribution, presumably caused by bilaterial compression of the internal carotid arteries in the neck during version and extraction.

A statistical analysis of this series leaves the firm impression that historical evidence of perinatal trauma correlates fairly closely with characteristic pathologic sequelae observed in postmortem studies. Acceptance of these findings as pathognomonic of the effects of birth trauma may be subject, however, to the following reservations:

(1) A traumatic birth history is not absolute proof of a cause-and-effect relationship in the resulting mental subnormality. For example, a history of maternal or fetal abnormalities at the time of birth was also recorded at times in cases of malformation, although in this group the abnormal circumstances were much less common and were relatively mild. On the other hand, in 7 percent of cases with typical lesions of perinatal trauma the birth history appeared to be negative.

(2) These data on institutionalized patients in whom the postmortem findings were weighted in the direction of severe grades of mental retardation may or may not apply to the entire population of mental subnormality, the role of birth trauma in lesser degrees of mental deficiency being largely unknown. According to Penrose, however, the neurologic signs of birth injury are scattered over all levels of intelligence. One can expect that lesions limited to some extrapyramidal nuclei, for example, may be associated with cerebral palsy in the absence of significant mental changes.

Pathogenesis

A number of different theories on the mechanisms involved in birth trauma have been advanced. Little described asphyxia neonatorum, but he did not discuss the reasons for such an occurrence that would distinguish the normal from the pathologic birth process. Schwartz believed that the difference between the intrauterine and atmospheric pressure was a cause of venous disturbances resulting in hemorrhages and softenings, and that asphyxia played a subordinate role. Marburg and Casamajor agreed with the assumption of a venous mechanism. Gruenwald, and more recently Towbin, regarded the immaturity of the nervous tissue in the vicinity of the ventricles to be a precondition for the development of the lesions in the territories of the deep veins, especially in the premature. Gillilan commented on a general lack of appreciation of lesions resulting from intracranial venous obstruction.

Other investigators such as Walsh and Lindenberg, Banker and Larroche, Abramowicz et al, emphasized disturbances in arterial circulation. They attributed the lesions in part or entirely to disturbed circulation in arterial border zones, brought about by such factors as left-sided cardiac failure and states of hypotension. Incisural herination from increased intracranial pressure has been favored by Earle, et al, to explain lesions in territories supplied by the posterior cerebral arteries. Courville emphasized anoxia in the immediate postnatal period as the fundamental process. But Penrose noted the difficulty of separating the effects of asphyxia from those of mechanical injury.

It had been hoped that experimental work would further elucidate the pathogenesis of birth trauma. Thus far, however, experimental asphyxia produced in animals at birth has resulted in lesions that in many respects differ from those attributed to fetal brain damage in human beings. Windle reported primarily cellular changes in diencephalic and brain stem structures. More recently, Myers produced asphyxial changes in the newborn monkey that he compared with lesions observed in clinical material. Such changes, he concluded, could be induced only under conditions of prolonged partial asphyxia, and elevated venous pressure might play a role in the pathogenesis.

A more precise assessment of the role of birth trauma in mental retardation may be enhanced by investigations along the following lines: (1) acquisition of accurate clinical data in prospective and retrospective studies; (2) correlation of clinical and pathoanatomic data in large series of cases; (3) comparison of the pathologic findings at various stages, permitting a more accurate outline of the sequence of events from acute to chronic phases; and (4) experimental reproduction of the clinical conditions.

Postnatal Trauma

Direct injury to a child's brain by falls or other accidents is an uncommon cause of mental retardation. In our series of 2,357 cases, there were eight instances (0.34 percent) of mental retardation due to postnatal trauma. These were patients who, following a normal birth and early development, sustained head injuries at ages ranging from two months to three years. For the most part, these children were involved in auto accidents, suffered skull fractures, and experienced initial periods of coma. The resulting mental retardation ranged from severe to mild and was variously associated with quadriplegia, hemiplegia, or epilepsy. The pathologic findings showed the characteristic sequelae of head trauma subdural hematomas, subarachnoid hemorrhages, and contusions—and thus did not differ essentially from post-traumatic lesions of adults. These findings agree with those reported in the literature.

REFERENCES

Abramowicz, A., Twitchell, T. E., and Yakovlev, P. I. The topographic pattern of status marmoratus in the cerebral cortex in double athetosis; its possible relation to the arterial "border zones" of the brain and its pathogenetic implications. *J. Neuropath. Exp. Neurol. 20:* 296–297, April 1961.

Alexander, L. The fundamental types of histopathologic changes encountered in cases of athetosis and paralysis agitans. *Res. Publ. Ass. Res. Nerv. Ment. Dis.* Williams and Wilkins, Baltimore, *21:* 334–493, 1942.

Anton, G. Uber die Beteiligung der grossen basalen Gehirnanghen bei Bewegungsstörungen und inbesondere bei Chorea. *Jahrb. f. Psychiat. 14:* 141–181, 1895.

Banker, B. Q., and Larroche, J. C. Periventricular leukomalacia of infancy, a form of neonatal anoxic encephalopathy. *Arch. Neurol. 7:* 386–410, Nov. 1962.

Benda, C. E. *Developmental Disorders of Mentation and Cerebral Palsies.* Grune and Stratton, New York, 1952.

Clark, D. B., and Anderson, G. W. Correlation of complications of labor with lesions in the brains of neonates. *J. Neuropath. Exp. Neurol. 20:* 275–278, April 1961.

Courville, C. B. Antenatal and paranatal circulatory disorders as a cause of cerebral damage in early life. *J. Neuropath. Exp. Neurol. 18:* 115–140, Jan. 1959.

Earle, K. M., Baldwin, M., and Penfield, W. Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. *Arch. Neurol. Psychiat. 69:* 27–42, Jan. 1953.

Gillilan, L. A. The arterial and venous blood supplies to the forebrain (including the internal capsule) of primates. *Neurology 18:* 653–670, July 1968.

Gruenwald, P. Subependymal cerebral hemorrhage in premature infants and its relation to various injurious influences at birth. *Amer. J. Obstet. Gynec. 61:* 1285–1292, June 1951.

Little, W. J. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum on the mental and physical condition of the child especially in relation to deformities. *Trans. Obstet. Soc. London 3:* 293, 1862.

2

Malamud, N. Sequelae of perinatal trauma. *J. Neuropath. Exp. Neurol. 18:* 141–155, Jan. 1959.

Malamud, N. Pattern of CNS vulnerability in neonatal hypoxemia. In: *Selective Vulnerability of the Brain in Hypoxemia.* J. P. Schade and W. H. McMenemey (eds.), Blackwell Scientifiic Publications, Oxford, 1963, pp. 211–225.

Malamud, N., et al. An etiologic and diagnostic study of cerebral palsy. *J. Pediat. 65:* 270–293, Aug. 1964.

Marburg, O., and Casamajor, L. Phlebostasis and phlebothrombosis of the brain in the newborn and in early childhood. *Arch. Neurol. Psychiat. 52:* 170–188, Sept. 1944.

Meyer, A., and Cook, L. C. Etat marbré. *J. Neurol. Psychopath. 16:* 341–352, April 1936.

Myers, R. E. Atrophic cortical sclerosis after asphyxia of newborn monkey. *J. Neuropath. Exp. Neurol. 27:* 126, Jan. 1968.

Norman, R. M. *État marbré* of the corpus striatum following birth injury. *J. Neurol, Neurosurg. Psychiat. 10:* 12–25, Feb. 1947.

Norman, R. M. *Malformations of the nervous system, birth injury and diseases of early life in neuropathology.* Williams and Wilkins, Baltimore, 1963.

Penrose, L. S. *The Biology of Mental Defect.* Grune and Stratton, New York, 1963.

Scholz, W., Wake, J., and Peters, G. Der Status marmoratus ein Beispiel system ahnlicher Hirnveränderungen auf der Grundlage von Kreislaufstörungen. *Ztschr. f.d. ges. Neurol. u. Psychiat. 163:* 193–232, 1938.

Schwartz, P. Birth injuries of the newborn. Morphology, pathogenesis, clinical pathology and prevention of birth injuries of the newborn. *Arch. Pediat. 73:* 429–450, Dec. 1956.

Schwartz, P. *Cerebrospinal birth injury: Types, causes, pathogenesis, consequences, and prevention.* Proc. 1st Intern. Med. Conf. on Mental Retardation. Grune and Stratton, New York, 1960, pp. 132–166.

Towbin, A. Cerebral intraventricular hemorrhage and subependymal matrix infarction in the fetus and premature newborn. *Am. J. Path. 52:* 121–140, Jan. 1968.

Vogt, C., and Vogt, O. Status marmoratus. *J. Psychol. u Neurol. 25:* Erg. 3, 1920.

Walsh, F. B., and Lindenberg, R. Hypoxia in infants and children: A clinical-pathological study concerning the primary visual pathways. *Bull. Johns Hopkins Hospital, 108:* 100–145, Feb. 1961.

Windle, W. F. Neuropathology of certain forms of mental retardation. *Science, 140:* 1186–1189, June 14, 1963.

Wolf, A., and Cowen, D. The cerebral atrophies and encephalomalacias of infancy and childhood. *Res. Publ. Ass. Res. Nerv. Ment. Dis.* Williams and Wilkins, Baltimore, *34:* 199–330, 1954.

GENERAL ASPECTS OF THE PATHOLOGY OF CRANIAL TRAUMA IN INFANTS AND CHILDREN

RAYMOND D. ADAMS, M. D., and MARIA Z. SALAM, M.D.
Joseph P. Kennedy Laboratories of the Neurology Service
Massachusetts General Hospital
The Research Laboratories of the Walter E. Fernald School
And the Department of Neuropathology and Neurology
Harvard Medical School

The central issue to be discussed is the extent to which physical trauma causes destructive lesions, and whether the control or prevention of such trauma would hold promise of significantly reducing the incidence of mental retardation.

It might also be helpful to indicate the extent to which some of the better known early and late sequelae of neurologic diseases of infancy and childhood, identified pathologically, may be justifiably ascribed to cranial traumatism. This is essential to any statistical survey of the incidence of cranial traumatism, and the designing of preventive measures could hardly proceed without it.

The Types of Cranial Trauma

Cranial traumatism ordinarily does not raise difficulty in diagnosis. It is the most obvious of all diseases because the causative event is so definite. The pathologic process is brief, the major part lasting seconds or at most minutes. The immediate medical problem consists essentially of preserving life and counteracting the complications of impaired cerebral function. The glaring exception to this clinical rule is the principal group of cases we are here considering—trauma incurred during parturition.

Cranial trauma can be divided into three major types, according to mechanism: (a) penetrating injuries; (b) blunt acceleration-deceleration injuries; (c) compressive-distortive injuries.

Penetrating Injuries happen relatively infrequently in civilian life. They involve high velocity missiles that strike the cranium with such force as to break the skull and tear asunder the meninges and brain. Immediate and fatal hemorrhage is the usual result, though lesser degrees of bleeding are compatible with survival. While injuries of this type occur accidentially in childhood, they are so infrequent as to be of little interest to members of a conference on mental retardation.

Blunt Acceleration-Deceleration Injuries, the common type in civilian life, have been the most thoroughly studied, and most of the published descriptions are devoted to this subject. The milder degrees of acceleration of the stationary head by a blunt striking force or deceleration of the rapidly moving head by an immovable surface cause only concussion. The dimensions of the responsible physical factors have been ascertained to exceed 32 ft/sec for the cranium of the macaque. Although defined clinically as a reversible physiologic change, manifest principally as an abolition of consciousness in the intact animal, and loss of additional reflex functions in the normal and anesthetized animal, it may nonetheless prove fatal. The pathologic basis of this state continues to be disputed. Claims for chromatolysis of neurons of brain stem and cerebral cortex (Windle, et al.) for shattering of myelin sheaths in the cerebral white matter (Strich) remain unverified. There is a high degree of reversibility pathology located most likely in the reticular formation of upper brain stem.

Difficulties in recognizing the morbid anatomy of concussion arise from the fact that reversible states nearly always reside in molecular or subcellular changes not to be seen with the light microscope, and also that increasing intensity of acceleration or deceleration of the unfixed cranium is attended regularly by another order of visible lesions, especially at the point of impact (coup) and opposite to it (contrecoup). Cortical necrosis, hemorrhage from small vessels, and even laceration characterize these lesions which are essentially contusions. Small hemorrhages occur also in the meninges and brain especially along lines of force extending inward from the point of impact and in the upper brain stem. These obvious lesions change with time, the contusion being converted to plaque jaune, the superficial cortical and subcortical necroses resulting in secondary tract degenerations which can be followed into the cerebral white matter, brain stem, and the larger intracerebral hemorrhages becoming brown-walled cavities. Meningocerebral cicatrization is another late formation, relating to concomitant meningeal injury with collagenous repair. Early functional deficits are traceable to traumatic paralysis (the pathological equivalent of concussion) and are highly reversible if time permits. Permanent residua are due to cortical-subcortical tissue deficits, and to ischemic lesions (infarcts) caused by compression of vessels incident to tentorial and other herniations of brain. Communicating hydrocephalus secondary to subarachnoid hemorrhage has been another frequent sequel and has accounted for a considerable number of our cases of normal pressure hydrocephalus in both adult and child. Epilepsy, one of the more important complications of the cortical lesions (25-40 percent of cases) is believed to constitute a special problem in that seizures alone may lead to an encephalopathy. Skull fracture occurs in the majority of cases and may pass through bony foramina where it can damage a cranial nerve. Unusual extensions of fractures may break the walls of sinuses or mastoid cells and permit escape of cerebrospinal fluid (CSF) and entrance of air or bacteria.

Lesser degrees of injury, sometimes not of sufficient force to cause concussion, may tear dural arteries and subdural veins, resulting in epidural and subdural hemorrhages. These may occur as isolated phenomena or as part of the picture of more severe concussive and coup-contrecoup types of cranial injury. Surface bleedings create problems all of their own, related essentially to cerebral displacement, herniation, arterial compression and secondary brain stem hemorrhages.

A special type of pathology is represented by traumatism of the carotid artery or its branches. In some instances a dissecting aneurysm may develop, leading to immediate or delayed occlusion and massive infarction of a cerebral hemisphere. Delayed hemorrhage (Spatapoplexie) stands as another poorly understood complication of cranial trauma.

The infant or child is presumably no more or less susceptible to blunt injury than the older individual. As in all instances of this type of trauma, cranial injury, in order to affect the brain, must reach a certain magnitude and we have no quantitative data as to whether this is greater or less than in the adult. All varieties of blunt injury are seen in the "battered child syndrome," and in children who have fallen onto hard surfaces or who have been involved in vehicular accidents. As in adult acceleration-deceleration injuries, such cases raise many vexatious problems which remain largely unsolved, such as the physical basis and mechanism of concussion, the pathogenesis of hemorrhage in the contusion syndrome, the pathogenesis of the diffuse brain swelling, the effect of regional necrosis and brain swelling on blood vessels, the mechanism of brain stem hemorrhages, and the pathophysiology of the cortical lesions that become epileptic foci. But these problems are in no way peculiar to infant or child, with the one exception of the diffuse cerebral edema, which is seldom observed at any other age. Our impression is that this latter condition depends in some manner upon the special incompetence of the child's nervous system to make an appropriate response (secretion of antidiuretic hormone) to the intake of parenterally administered fluids.

Compression-Distortion Injuries, in contrast to penetrating injuries and blunt acceleration-deceleration injuries, are characteristic of only one period of life, coinciding with parturition when the cranial sutures are still ununited. Comparable degrees of compression of the skull rarely occur in postnatal life. Should it happen later, the skull must be virtually crushed before the brain suffers injury and then there is a set of pathologic changes of somewhat different type. The inapplicability of most of our factual information about head injury of adult man to that of infancy is explained essentially by the differences between blunt acceleration-deceleration and cranial compression-distortion injuries.

The literature on this type of injury is distressingly meager, and what is known gives an incomplete picture of what happens. The observations of Pollailon, Schatz, and Westmark, who measured intrauterine pressures of 200–400 mm of Hg during labor pains, and the still more precise recordings by Caldeyro-Barcia, give some notion of the magnitude of the forces involved. The violence is more generally evidenced by inspection of the heads of recently born infants, with their distortions, indentations, caput succedaneum, and cephalohematomas. Egg-shell fractures have been repeatedly documented, especially in forceps deliveries. Two other signs of physical stress are: (1) over-lapping of sutures (determined by palpation of the head and direct visualization of postmortem examination) due to the contractile force of the muscular uterine wall and in some instances favored by general cephalo-pelvic disproportion, and (2) base-vertex and anterior-posterior distortions due to disproportion between the lateral and perpendicular pressure in the space into which the advancing cranium is forced.

The following immediate effects of these physical deformations of the cranium have been recognized:

1. *Subarachnoid hemorrhage, presumably from the injury of meningeal vessels.* This is the most frequent and seemingly the most innocent. Den-

in, Billard, and Cruveilhier recognized its importance as early as the beginning of the 19th century. Demonstrable during life by lumbar puncture, which has been routinely and skillfully performed in several series of several hundreds of cases, a variable number of red blood count (RBC) and hemosiderin (xanthochromia) with appropriate leucocytic reactions and increased protein have been revealed in approximately 10 percent of normal births and in a higher percentage of premature ones and in others following prolonged labor. The precise source of leptomeningeal hemorrhage is not settled, even in the fatal cases, nor are the long-term effects of more severe subarachnoid hemorrhage know in survivors.

2. *Dural Tears (tentorial and falcial) and subdural hemorrhage.* Known in neuropathology as the Beneke lesion, after the pathologist who first described them, they are related not to over-riding of cranial bones but to vertical or fronto-occipital deformation of such degree as to exceed the elasticity of dura. Kundrat pointed out the frequent tearing of cerebral veins at points where they entered the dural sinuses and of the sinuses themselves, especially when stiffened by intense venous congestion.
3. *Intracerbral and intraventricular hemorrhages.* In all series of autopsies in the neonatal period, whether death was due to respiratory distress or to intracranial disorder, hemorrhages in the matrix zone and adjacent ventricle have been frequent (approximately 10 percent of cases). In most instances these must occur in the agonal period since there is seldom any reaction around them even if the infant has survived for several days after birth. It is especially difficult to evaluate them if the patient has lived only a few hours, being then perhaps impossible to distinguish postmortem artefact from true lesion with any degree of reliability.
4. *Leucomalacia.* Infants who have lived for some days have shown an impressive number of infarcts deep in the white matter. Observed first by Virchow, who misinterpreted them as foci of congenital encephalitis; later regarded as venous infarcts due to circulatory stagnation by Schwartz, Meyer, Banker and Larroche have more recently postulated an inadequacy of arterial circulation. Of all the cited lesions, their relation to physical trauma remains the most controversial. The frequent association of this lesion with necrosis of the cerebral and cerebellar cortices and basal ganglia suggests an hypoxic or ischemic basis.
5. *Tearing and occlusion of neck vessels.* Here reference is made to the frequent injury to neck vessels, especially the vertebrals, as will be discussed later by Professor Yates.

Exceptionally, infants who have survived such traumatic births have died after an interval of time sufficient to permit the clinical effects of the cerebral lesions to become evident and the pathologic changes to be viewed in their more chronic stages. Hemosiderosis and thickening of the leptomeninges, encapsulated subdural hematomas, periventricular cavities and disappearance of laminae of cerebral gray matter are then the usual findings. But what is most remarkable has been the unexpected differences between these immediate effects of birth trauma and hydrocephalus and the more common encephalopathies that underlie mental retardation, cerebral palsy, and epilepsy. These discrepancies are so pronounced as to call into question the relationship between birth trauma and the major diseases of the child's cerebrum.

A more careful consideration of the pathophysiology of the traumatic cerebral lesions of parturition suggests that the main factors of circumferential compression of the cranium must lead to overlapping of the flat bones of the vertex and diminution of intracranial volume. The possibility of such forces tearing thin-walled turgid vessels and letting blood escape into the subarachnoid and subdural space requires no imagination. With a rise in intracranial pressure, the effectiveness of the buffering action of the CSF might be reduced and the cerebral tissues could suffer direct injury.

Whether or not the obliteration of the subarachnoid space and firm application of cranial bone against cerebral surface vessels could compromise the circulation has not been investigated, to the best of our knowledge, but perhaps our colleagues know of such studies. It seems to us unlikely that this could happen because if one looks at the cortex beneath a large subdural hematoma, ischemic effects are seldom found. Indentation of a part of a cranial bone or its fracture, as by the placement of a forceps blade, will, or course, bruise an area of brain or tear surface arteries or veins, resulting in an epidural or subdural hemorrhage. (In fact, in rare instances cerebral trauma has been sustained by a direct blow to the abdomen of the pregnant woman.)

Another unsettled matter is whether elongation of the malleable head, putting falx and tentorium on stretch, results in ischemia of the brain by occlusion of the venous sinuses, which they enclose, or exposed blood vessels.

Raised intracranial pressure above and around the cerebrum could surely force the nervous tissue down against the floor of the anterior and middle cranial fossae and down through the opening of the tentorium into the posterior fossa. Earle, Baldwin, and Penfield showed how this could happen in a postmortem human specimen but their test (putting a tight elastic around the cranium) hardly duplicates conditions during life. It was from general analogy with mass lesions and regional increases in pressure in more mature brains that led them to postulate a mechanical effect to cause foci of infarction and thus to explain the common sclerosis of hippocampi, orbital frontal, polar temporal cortex and amygdaloid nucleus observed in many of their cases of temporal lobe epilepsy. However, it must be noted that they did not succeed in finding a true temporal lobe-tentorial herniation in a single case of birth trauma and many of the lesions in their surgical series which were ascribed to this mechanism were localized in parts of the brain whose vascular supply is not ordinarily compromised by such herniations in later life. Purely speculative is their postulation of downward pressure occluding not merely branches of the posterior cerebral arteries but anterior choroid, posterior communicating and middle cerebral. Norman et al have espoused this mechanism in birth injury and cite cases of parieto-occipital sclerosis as proof of an entrapment of posterior cerebral arteries. But a review of their cases shows many of the lesions to be in the border zone between cerebral arteries rather than end-zone of this artery, which suggests the operation of a more generalized circulatory disorder. Of course, one might contend that in compressive-deformative injuries which alter the shape of the cranial cavity, the mechanics might be such as to jeopardize more anteriorly situated arteries. Similarly, the proposition that a combination of mechanical distortion, hypotension, and hypoxia might exert unpredictable effects in the neonatal brain remains Q.E.D. It is entirely plausible that ischemia and hypoxia, acting together, could induce lesions when either one alone would be ineffective.

The traumatic origin of intracerebral and intraventricular hemorrhages is far less clear. In the majority of our cases they have occurred as isolated events, often in conjunction with hypoxic necrosis of the cortex or central white matter rather than with traumatic meningeal hemorrhage. Matrix hemorrhages, the common type in the premature brain, deserve separate consideration. They often happen some days after birth and appear more clearly linked to terminal circulatory failure and hypoxemia than to trauma. In only a few instances is there an associated ischemic necrosis of cerebral cortex, white matter or basal ganglia, and many of these are agonal, i.e., transpire in the last hours or day of life. Older lesions of this type, in infants dying later, are extremely rare. The hemorrhages seem to be linked to death.

Evaluation of Encephalopathic States Which Have Been Ascribed to Birth Trauma

Since the effects of parturition on the brain are difficult to measure, it is common practice to denominate by the term "birth trauma" all pathogenic states happening in early life, whether from the application of physical force to the fetal head, arrest of circulation to all or part of the brain, hypoxia, or other causes. Norman and his associates rightly point out that it is almost impossible to separate trauma from circulatory disturbance, especially if one concedes that trauma may injure or occlude blood vessels. The obscurity of these disease states has, however, retarded understanding of the basic abnormalities and their prevention.

The following lesions in the infant or child's brain have been attributed to birth trauma:

A. BIATERAL OF UNILATERAL ENCEPHALOMALACIA WITH NECROSIS OF CORTEX AND WHITE MATTER

This type makes up the majority of the patients in which severe mental retardation, convulsive state, bilateral or unilateral spasticity or rigidity, with or without chorea or athetosis, are manifest from the early weeks or months of postnatal life. Seizures are present in nearly all cases. Survival may be for months or years, depending to some degree on the severity of lesion and degree of disability. Cortical necroses, ulegyria, lobar sclerosis, cortical-subcortical encephalomalacia are present to varying degrees in combination with cavitation or atrophy of caudate and lenticular nuclei, thalami and loss of neurons in cerebellum.

Of the cases in the medical literature, including our own, that illustrate this condition one learns that some patients have been difficult to resuscitate at birth while others have had a relatively normal birth and early development with later onset of the cerebral lesions during an acute convulsive febrile illness. Asymmetry of cerebral affection explains the unilaterality of predominant neurological signs.

Again causation remains uncertain. Regional circulatory insufficiency must be invoked as the basic mechanism but more diffuse nerve cell loss in cerebrum and cerebellum suggests an hypoxic factor. Traumatism alone cannot be seriously considered, nor can brain swelling with herniation and compression of vessels. Some of the cases unquestionably have lesions that develop during the parturitional period. The lesions while essentially of vascular type, probably do not have a single origin, and other conditions, such as inflammatory diseases, are included. But, the vascular ones, unlike vascular diseases of adult life, are usually accompanied by diffuse hypoxic changes. Some of the lesions fall principally in the water-shed areas between the cerebral vascular territories.

B. Multiple Cystic Leucoencephalopathy

This lesion in which a large portion of the white matter is destroyed and replaced by irregularly shaped cavities, some communicating with lateral ventricles, has also been called "cystic transformation of the brain," "pseudocystic brain," "disseminated leukomalacia with cavitation," "porencephaly of white matter," or "polyporencephaly."

Causation is obscure. A survey of reported cases shows once again that ambiguous definition of the pathologic state is the source of some confusion. One group, by far the larger, includes cases in which the destructive process, while involving both gray and white matter, resulted in prominent cavitation of white matter. All three of the cases illustrated by Wolf and Cowan, and several of those of Benda, were of this type. Their clinical history was that of an infant who had suffered a prolonged and difficult labor and was recognized as abnormal in the neonatal period, i.e., was irritable, convulsing, and unable to feed properly. Psychomotor retardation, emerging spastic quadriparesis, blindness, deafness, and small cranium with early closure of sutures characterized the later clinical picture. Essentially this form of cerebral disorder is one of global encephalomalacia with cavitation of central parts of the brain; the neuronal loss in cerebellum is of hypoxic type. Trauma in the strict sense could not account for this type of encephalopathy, and although hypoxia incidental to birth might be a factor, the lesions are of such magnitude as probably to require a general arrest of cerebral circulation.

Such cases raise the whole question of white matter infarction during circulatory arrest and vascular occlusion. Infarcts predominantly in the white matter are occasionally observed in adult men consequent to major artery occlusion. But, nearly always the cortex is involved to some degree. The greater extent of the white matter involvement has been explained as a marginal or water-shed effect at the interface between the deep penetrating ganglionic and cortical arteries (Meyer) but the details have never been worked out. In the infantile brain, Banker and Larroche invoke this mechanism whereas Schwartz has claimed Galenic vein congestion and thrombosis, again without anatomical proof.

In a second group, there is complete sparing of the gray matter. Ford, who cites examples, makes the point that this condition develops postnatally, usually within the first year, and is progressive. Unilateral and then bilateral hemiplegia or quadriplegia from the onset, recurrent convulsions going on to cortical deafness and blindness, i.e., total decerebration, constitutes the clinical picture. The CSF is unremarkable. Death has usually occurred within a few months. Viral infections, or a degenerative or metabolic disorder are hypothesized; the evidence for or against them need not be reviewed here.

C. Mantle Sclerosis

In this condition, called congenital microgyria with diffuse sclerosis, progressive sclerosing cortical atrophy or hemiatrophy, progressive infantile poliodystrophy, and cerebral dysplasia, the brain is found reduced in size owing to enormous loss of neurons in all parts of the cerebral cortex, cerebellar cortex, and basal ganglia. They are replaced by astrocytic glia, giving the brain a shrivelled appearance and unnaturally firm consistency. The brain looks like the kernel of a walnut.

Alpers has reported cases of this type in which the disease began in childhood, long after birth, and was progressive over months and years, and Christensen has written about others. Multiple involvement in one sibship has been observed. The disease is in a sense akin to Jakob-Creutzfeld's disease except for its early onset. However, a survey of published cases, e.g., series of Wolf and Cowan, and Benda, shows that every group includes examples of widespread destruction of gray matter of abrupt onset without progression and with lesions analogous to those of severe hypoxia due to cardio-pulmonary failure. The reason for the confusion stems from the difficulty in pathological characterization of diseases from a study of their end-stages.

Assuming that we are concerned here only with the form that destroys the cerebral gray matter over a brief period of time at or near the time of birth, one occasionally finds instances of disease where the gray matter is affected more or less exclusively. One notes that the reduction in size of cerebral convolutions depends on severity of nerve cell loss and length of survival. The narrowed cortex, poorly distinguished from underlying white matter, exhibits at times a porosity or linear necrosis, and rarely are there even a few subcortical cavities. The lateral ventricles are symmetrically enlarged. Internal capsules, fornices and corpus callosum are atrophic and volume of cerebral white matter is diminished. The thalamic, caudate and lenticular nuclei may be of normal size, or reduced, and the cerebellum may share the same uncertain fate. As a rule, the midbrain, pons, medulla and spinal cord show no change other than smallness of corticopontine and corticospinal tracts. In some instances there are rusty-colored subdural membranes. Granular ependymitis may be present. The meninges are not remarkable and vessels are patent.

Seizures, weak cry, and poor motility may be present from birth or become evident later. Listlessness, dullness, apathy, poor feeding, irritability, restlessness, delay in all motor attainments, lack of a definite visual and auditory response, recurrent infections, spastic weakness and Babinski signs combine to form a "decorticate state." The CSF is normal or with elevated protein. The average period of survival is 4–6 months.

The birth history and pathological findings in this nonprogressive form of mantle sclerosis are all compatible with a brief period of hypoxia at about the time of birth. A vascular factor seems improbable because the lesion is not one of ischemic necrosis. Only if the changes are unilateral (hemiatrophy of cerebrum) does an additional factor of circulatory impairment seem at all likely. The possibility of physical trauma can be definitely excluded because the diffuse involvement of cerebrum and cerebellum corresponds not at all to any known traumatic lesion. The proposal that trauma could cause epilepsy and the epilepsy could result in postepileptic encephalopathy is untenable because of the absence of such cortical changes in most cases of idiopathic epilepsy. Nor could high intracranial pressure and tentorial herniation with vascular occlusion explain this lesion. Exceptionally diffuse hypoxic encephalopathy has followed status epilepticus. One notes, however, that of all the reported cases of pure polioencephalopathy relatively few date from a specific early hypoxic episode. Most represent another type of disease, a progressive metabolic or slow viral encephalopathy.

D. Status Marmoratus (État Marbré)

Zones of neuronal loss and gliosis and aberrant growth of medullated fibers in the pulvinar and posterolateral nucleus of thalamus, and the cerebral cortex (usually in border zones between the anterior, middle and posterior cerebral arteries) combine to impart an effect of marbling, from which this lesion takes its name. The unique feature is the presence of bundles of medullated fibers presumably arising from the external capsule and adjacent white matter which are more numerous and densely packed than normal. In all of our cases a more diffuse neuronal loss has been found, usually in cerebral cortex (posterolaterally in the cerebral hemisphere), in the Sommer's sector of hippocampus, and in the deep folia of cerebellum. Severe asphyxia at birth, with delay in resuscitation, respiratory distress and cyanosis, are noted in most of the clinical records. Poor neonatal response, seizures, impaired control of vegetative functions, and early motor disturbances are recognized in many of the cases during the first month of life; and rigidity, spasticity, athetosis, seizures, psychomotor delay appear later in nearly all cases.

Although many articles on the pathology of the congenital encephalopathies give excellent descriptions of this condition, they fail to show the frequent overlaps between it and mantle sclerosis, sclerotic microgyria, and the other encephalomalacias. Its importance is the example it provides of a late malformation due to a lesion sustained at birth, which allows undamaged neurons and fibers to grow and develop in abnormal patterns. Probably the same may be said, however, of some cases of sclerotic microgyria.

E. Other Enchepalopathies: Disseminated Sclerosis Mainly in Temporal Lobes

Zones of infarction or focal nerve cell loss leading to cavitation or gliosis (sclerosis) have been found in various parts of the cerebrum, especially the temporal lobe cortex, amygdaloid nuclei and hippocampal formations. Such lesions are smaller and more disseminated than those of groups A and B. The clinical significance is due to their relationship to epilepsy of the temporal lobe type. Again, their greater extent in gray than white matter, the involvement of cortex in depths and on banks of sulci, the variable destruction of interstitial elements (viz., cavitation) point to a vascular mechanism i.e., occlusion of small arteries or veins. Since the underlying disease is nonfatal, such lesions usually must be studied in an endstage long after their inception, and the vascular abnormality either has not been sought or is impossible to demonstrate.

The connection of these small focal gliotic zones to trauma remains dubious. As was stated above, Earle, et al, supposed that herniation of temporal lobes against the tentorium at the time of birth could occlude surface arteries, but the distribution of lesions outside the territory of the posterior cerebral arteries (the only basilar arteries exposed to herniation except rarely an orbital branch of an anterior cerebral artery which may be pressed against the lesser wing of the sphenoid bone) leads one to reject this mechanism. Simple pressure of a flat cranial bone against brain, as the head is molded, has never been proven; if it figures at all in the causation of this lesion some other factor such as diminished cerebral circulation or hypoxia must intervene. No better argument can be entertained for their etiology.

Conclusions

The main ideas which should emerge from this review are the following:

1. Penetrating and blunt acceleration-deceleration injuries of cerebrum do happen in infancy and childhood as well as adulthood causing concussion and a variety of contusions, meningeal hemorrhages, intracerebral hemorrhages and necroses and sequelae of variable severity. For the most part they are not a frequent source of mental retardation even when they occur at an early age.
2. There is nothing peculiar to acceleration-deceleration injury of brain in infancy and childhood except for a higher incidence of symptomatic regional cerebral edema. Moreover, the pathology of this type of injury is well known, though admittedly there are many unsettled problems such as the nature and locus of concussive injury, the validity of primary myelin damage as a component of it, and the mechanism of post-traumatic hydrocephalus.
3. The unique feature of birth injury, the form of traumatism most relevant to mental retardation, is that it depends essentially on compression and distortion of the cranial vault at a time when the source of cerebral circulation is changing from the mother to infant and before sutures have united. As an obvious corollary, data concerning acceleration-deceleration injuries are therefore inapplicable to birth injury.
4. Subarachnoid subdural hemorrhage, dural tears, and matrix hemorrhages, the acknowledged consequences of compressive-distortive birth injuries, appear to have at most an indefinite relationship to the lesions of brain-injured survivors. Evidently the meningeal hemorrhages resolve and old intracerebral ones rarely are found in this group of patients who survive for a time.
5. Whether vascular lesions, also frequent in this age period, are related to trauma has not been determined. Claims for compression of cranial arteries incident to high intracranial pressure are unsubstantiated. Intracerebral (matrix) hemorrhages appear to be more the result of hypoxia than of direct trauma. There is no evidence of an infantile hydrocephalus that results regularly from meningeal hemorrhage at birth but perhaps this is being overlooked.
6. When the common encephalopathies (regional encephalomalacia, dis-

seminated leucomalacia with cavitation, white spot disease, mantle sclerosis, status marmoratus, and disseminated focal cortical necrosis) which begin at or soon after birth are reviewed it becomes obvious that there is no evidence that physical trauma at birth is the sole factor operating in any of them. Further, the grouping or classification based alone on end-stage pathologic pictures is so inexact as to include progressive diseases as well as fixed, nonprogressive ones. In all of these, vascular and hypoxic factors appear to predominate, which explains why the main pathoanatomic patterns of those existing from the time of birth seldom occur in pure form. A review of these several types of pathologic change in children who have been through a catastrophic parturitional experience reveals that in all of them there are: a time course which is brief and monophasic; pathologic change which is destructive of normally-formed brain tissue, combining regional pannecrosis with more diffuse neuronal loss; unique forms of resolution and repair, resulting in cavitation, gliosis, and aberrant growth of medullated fibers; and distribution of lesions within the territories of arteries or the border zones between them. Ischemia and hypoxia rather than trauma appear to be the most plausible pathogenetic mechanisms.

There is need of experimental investigation of the physical forces to which the cranium of the parturient infant is subjected and of the effect on cerebral circulation and oxygenation.

DISCUSSION

Dr. Dodge: Doctor Malamud mentioned the recent work of Ronald Meyers and his associates, Drs. Brand and Adamson. I think these studies of the sequelae of neonatal hypoxia in the monkey represent an important step in the development of an experimental model essential to the study of abnormal processes in the perinatal period.

This model involves reduction of maternal blood pressure and, as a consequence, fetal oxygenization, during the latter portion of pregnancy and in the neonatal period. The investigators prolong this for a matter of hours, and demonstrate a striking swelling of the posterior, lateral portions of the occipital parietal lobes, the central regions and the precentral areas. These lesions frequently are associated with the hemorrhagic process, and hemorrhagic infarction in these structures.

By very careful nursing of these animals, the investigators have been able to achieve prolonged survival and have witnessed the development of what to me is essentially identical with the disorders described by Dr. Malamud this morning. I think such a model may serve as an opportunity for a more careful study of physiologic and physical parameters as well as of the consequent patho-anatomic changes.

Dr. Barlow: There are a number of people with relatively fixed motor defects who go through a life of apparent nonprogression until some time in adolescence or early adult life when their defect undergoes a period of progression.

I've seen this on a number of occasions. I'd like to ask Dr. Malamud, in particular, whether this extensive material of his would give any hint of the reason for this.

Dr. Adams: We had one rather remarkable case that bears on your question, Dr. Barlow: a woman, aged 55, who developed an intention myoclonus in her right leg and in her right arm. The condition progressed for about five years. She had been entirely normal all of her life. We know that for certain. When she died, she was found to have had a congenital deficiency of her right cerebellar hemisphere. She had been that way all of her life; it was one of these cases where there had been compensation. But, then, why did she subsequently develop the myoclonus?

The whole question of whether the damaged nervous system will survive as well as normal, or tolerate aging effects as well as the normal, is a vexing matter that has been much discussed recently, but we have no data.

Dr. Churchill: I'd like to redirect your attention to the Earle, Baldwin, Penfield paper, where, by models, they showed that it was possible to herniate the temporal lobe, and also mentioned that direct contusion of the anteromedial surfaces of the temporal lobe may occur. Perhaps this latter possibility makes more sense in terms of the production of epileptogenic lesions. Now, if one occludes an artery, or arterial supply to the brain, one will have a sharply demarcated depopulation of the neurons and supporting white matter beneath it.

This type of lesion would be unlikely to act as an epileptogenic lesion. On the other hand, a cortical contusion would lead to an area of damaged neurons that would sustain viability but be injured, perhaps in such a way as to act as an epileptogenic focus.

In studies on temporal lobe seizures, we came to the conclusion that even after excision of some of these lesions, the focus of the epileptic lesion continues to advance. The study cited postulates that this occurrs by way of gliosis, which then would compress and constrict the small venules, causing stasis and congestion locally, which then, in turn, would produce more of a gliotic reaction; in such a way, the lesion would slowly progress over the years.

Shultz regards the situation somewhat similarly, and his laminar atrophy, if I'm not mistaken, relates to an interference with venous return, with the production of gliosis; he associates his laminar atrophy with epileptogenic potentialities. I'd like to ask Dr. Adams particularly, and Dr. Malamud also, whether one can perhaps dichotomize the two postulates—that a contusion with a very small venous occlusion may lead to epileptogenic lesions, whereas, arterial occlusions can lead to paralytic lesions without epilepsy.

Dr. Adams: As to the question of whether there are two types of lesions, one due to entrapment of arterial branches with ischemic necrosis in the cortex and subcortical white matter, I think that there has been no anatomical proof that such lesions occur within the territory of these vessels. This is the main argument I was presenting. In considering whether these babies could be sustaining contusions of the temporal lobe, we must recognize that these contusions, for the most part, have not been seen. As far as the ischemic necrosis is concerned, I should say that usually infarctions are hemorrhagic, because the occlusion is intermittent. The lesions that are being described are not hemorrhagic, they're usually sclerotic. As far as their epileptic potentiality, I would say that any cortical lesion has about the same epileptic potentiality.

The question of spreading gliosis and the failure of operation to stop an epileptic state is a very involved subject, and I don't think we can settle it quickly.

Obviously, if you produce another lesion while attempting to remove the epileptic lesion, you're fighting a losing battle, and it is a moot question whether the spreading gliosis itself is a factor leading to the epilepsy. I doubt it very much. I think it is some kind of a disequilibrium of cortical neurons which have an inhibitory function in the cortex.

REFERENCES

Alpers, B. J. Diffuse progressive degeneration of the gray matter of the cerebrum. *Arch. Neurol. Psychiat. 25:* 469–505, March 1931.

Banker, B. Q., and Larroche, J. C. Periventricular leucomalacia of infancy. A form of neonatal anoxia encephalopathy. *Arch. Neurol. 7:* 386–410, Nov. 1962.

Benda, C. E. The late effects of cerebral birth injuries. *Medicine 24:* 71–110, Feb. 1945.

Benda, C. E. *Developmental Disorders of Mentation and Cerebral Palsies.* Grune and Stratton, New York, 1952.

Caldeyro-Barcia, R. Compression received by the head of the human fetus during labor. This Symposium, 1968.

Christensen, E., and Krabbe, K. H. Poliodystrophia cerebri progressiva (infantilis). Report of a case. *Arch. Neurol. Psychiat. 61:* 28–43, Jan. 1949.

Earle, K. M., Baldwin, M., and Penfield, W. Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. *Arch. Neurol. Psychiat. 69:* 26–42, Jan. 1953.

Ford, F. R. *Diseases of the Nervous System in Infancy, Childhood, and Adolescence.* Charles C Thomas, Springfield, Ill. 5th ed. 1966.

Meyer, J. E .Uber die Lokalisation fruhkindlicher Hirnschäden in arteriellen Grenzgebieten. *Arch. Psych. u. Ztschr. Neurol. 190:* 328–341, 1953.

Nevin, N. C. Neuropathological changes in the white matter following head injury. *J. Neuropath. Exp. Neurol. 26:* 77–84, Jan. 1967.

Norman, R. M. Atrophic sclerosis of cerebral cortex associated with birth injury. *Arch. Dis. Child. 19:* 111–121, Sept. 1944.

Pollailon, Schatz, and Westmark. See Rydberg, E. Cerebral injury in newborn children consequent on birth trauma. *Acta Neurol. Psychiat. Suppl.* X. 1932.

Schwartz, P. Erkrankungen des Zentralnervensystems nach traumatischer Geburtsschädigung. Anatomische Untersuchungen. *Zeitschr. ges Neurol. Psychiat. 90:* 263–468, 1924.

Strich, S. J. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. *J. Neurol. Neurosurg. Psychiat. 19:* 163–185, Aug. 1956.

Windle, W. F. *Asphyxia Neonatorum.* Charles C Thomas, Springfield, Ill., 1950.

Wolf, A., and Cowen, D. The cerebral atrophies and encephalomalacias of infancy and childhood. *Res. Publ. Ass. Res. Nerv. Ment. Dis. 34:* 199–330, 1954.

DISTRIBUTION OF THE TERMINAL HEMORRHAGES IN THE BRAIN WALL IN STILLBORN PREMATURE AND NONVIABLE NEONATES

Paul I. Yakovlev, M.D. and Remedios K. Rosales, M.D.
Laboratories of Normal and Pathological Anatomy
and Development of the Nervous System
Warren Anatomical Museum
Harvard Medical School
Boston, Massachusetts

After the third lunar month, two distinct zones are recognizable in the wall of the cerebral hemisphere (fig. 1) —the deep zone, or *centrum semiovale* (*CS*), surrounding the corpora striata and the lateral ventricles and encased in a dense wickerwork of interlacing fiber bundles, and the superficial zone, or *corona radiata* (*CR*), with the cortical plate covering it. The reticulate wickerwork of fibers (*CS*), which surrounds the lateral ventricle and the corpus striatum, appears earlier and develops more rapidly than the radial fibers of the *corona radiata*. However, from about the fifth lunar month to term, with the continued growth of the hemisphere and surface expansion of the cortical plate, the corona radiata begins to gain in the tempo of growth and after birth exceeds, in both mass and in the width of cross section, the centrum semiovale in the core of the hemisphere.

The two zones differ not only in histoarchitecture, but also in the pattern of vascularization and in the hemodynamics of blood circulation. The centrum semiovale is supplied by the short circumferential arterial branches arising proximal to the origins of the three main cerebral arterial trunks. These short circumferential or lenticulo-striate arteries sprout earlier than the distal branches and are terminal arteries, without anastomoses.

The superficial zone is supplied by long circumferential branches of the main cerebral arteries (Klosovskii, vander Eecken). These branches develop later to supply the cortical plate and white matter of the corona radiata with abundant anastomoses in the cortical "border zones" between the terminal branches of the three main arterial trunks (Lindenberg and Spatz). However, in the zone of architectonic demarcation between the centrum semiovale and the corona radiata, the two arterial systems do not anastomose except through the capillary bed.

This study was supported by NIH Grant *NB*-03190. (Scheduled but not presented at the conference)

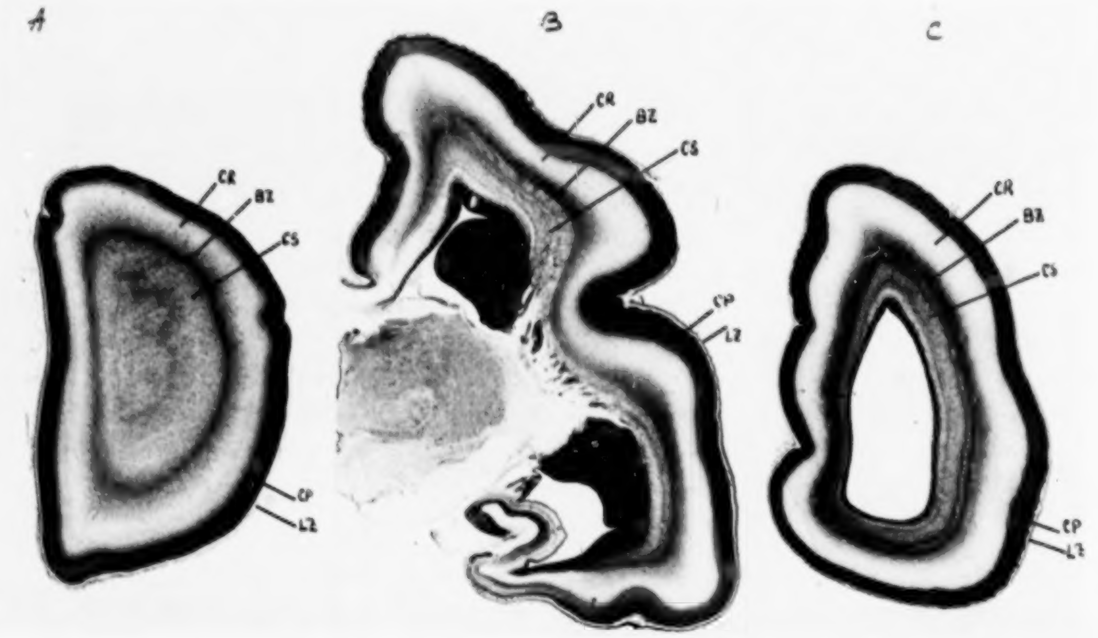


FIGURE 1.—Architectonic zones of the white matter in the wall of the cerebral hemisphere at four fetal months.

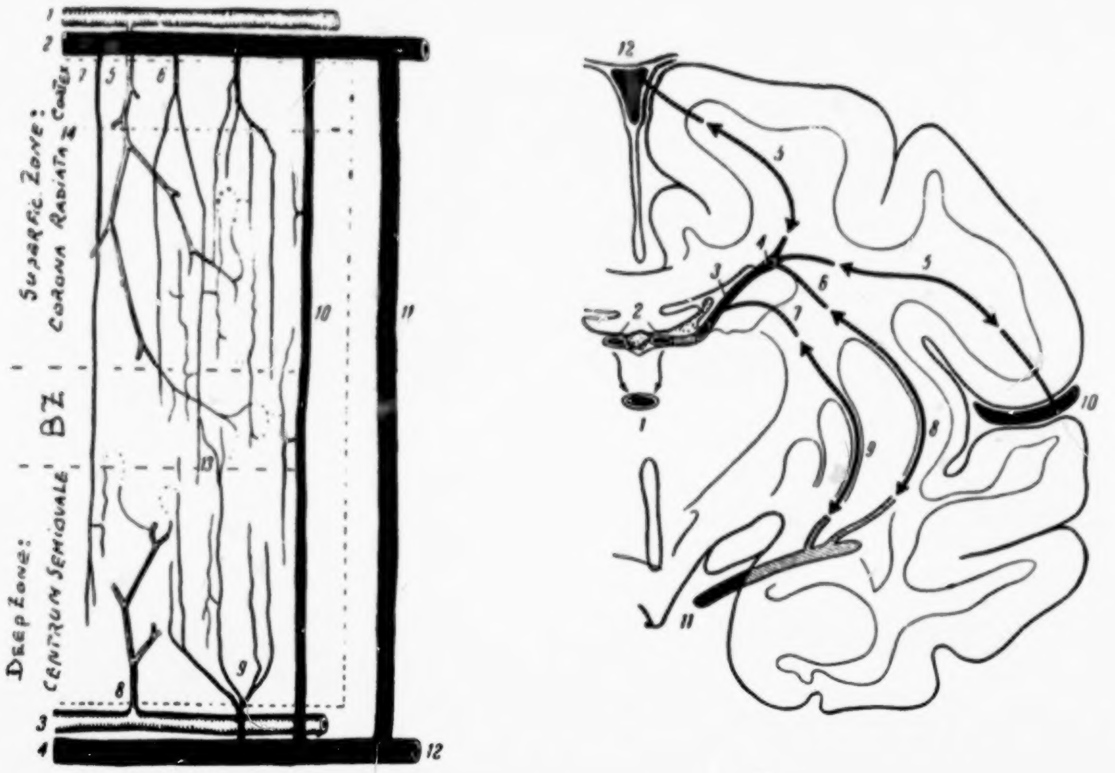
a: immediately anterior to the frontal horn of the lateral ventricle; b: at the level of hemispheric stalk and thalamus; c: the level of the occipital horn.

Abbreviations:

BZ—architectonic demarcation (or border zone) between *CR*—corona radiata and *CS*—centrum semiovale; *CP*—cortical plate; *LZ*—lamina zonalis (marginal layer).

The pattern of disposition of veins draining the two zones of the brain wall is also different (Schlesinger, Klossovsky). This is shown in Schlesinger's diagram (figs. 1a and b). The veins of centrum semiovale (internal cerebral veins) exhibit early and rich anastomoses and drain into the vein of Galen (Padget). The veins of the corona radiata develop later. These are straight veins coursing radially through the white matter of the cerebral hemisphere (fig. 2) and have few anastomoses in their course. They drain the corona radiata and cortex into the richly anastomosed superficial plexus of the superior cerebral veins. Between the deep and the superficial systems of cerebral veins there are large intramural anastomotic channels that penetrate the entire width of the brain wall and permit a rapid shunt of venous blood between the two systems of the cerebral veins. These intramural anastomotic veins are disposed concentrically (fig. 1b), in planes roughly tangential to the plane of the dense wickerwork of fiber bundles (fig. 3) which capsulate the centrum semiovale and demarcate it from the corona radiata. In this border zone (BZ), the vasculature of the two architectonically distinct layers of the brain wall consists mainly of the capillaries and small arteries and veins with only few and sparse anastomoses.

It is significant that extensive hypoxic leucomalacias in the premature and nonviable neonates occur most often in the deep zone and do not extend beyond


1
2
3
4
5
6
7
8
9
10
11
12
13
Superfic Zone: Corona Radiata & Cortex
BZ
Deep Zone: Centrum Semiovale
12
5
5'
4
3
2
1
6
7
8
9
10
11

a. b.

FIGURE 2.—Diagrams of anastomotic shunts between the deep and the superficial systems of cerebral veins. (Adopted from Schlesinger). a: A long circumferential (superficial) artery and a superficial cerebral vein are represented at 1 and 2; a short circumferential (deep) artery and a deep cerebral vein are represented at 3 and 4; the penetrating branches of these arteries and veins are represented respectively at 5 and 8 and at 6 and 9. Large intramural and extramural (superficial) anastomotic channels at 10 and 11 provide for a rapid shunt of blood between the two systems of veins. The radial veins (at 6, see also fig. 3) drain the corona radiata and cortex, and a few long transmural veins, such as at 7, drain the centrum semiovale (striatum) into the superficial veins. However, the centrum semiovale is drained mainly via deep veins such as at 9. In the transition zone (*BZ*), between the centrum semiovale and corona radiata, the anastomoses between the two systems of veins, such as at 13, are few and sparse. b: Schematic represention of the system of large intramural anastomotic veins disposed in the brain wall in three concentric tiers: these provide for a rapid shunt of blood between deep and superficial systems. The outermost tier of anastomotic veins represented in the white matter of the corona radiata at 5 and 5' connects the superficial Sylvian vein (10) and superior longitudinal sinus (12) with the system of deep (internal cerebral) veins (2, 3, 4) and vein of Galen (1); the intermediate tier of the *external* lenticular veins (6 and 8) and the innermost tier of the *internal* lenticular veins (7 and 9) in the core of the brain connect the basal Sylvian vein (11) with the system of deep cerebral veins. Note that each tier of these intramural anastomotic veins corresponds to a different architectonic layer in the wall of the forebrain (corona radiata-centrum semiovale-core); the anastomoses between tiers are few and the shunt of blood *across* the layers is minimal, mainly through the capillary bed of the brain wall.

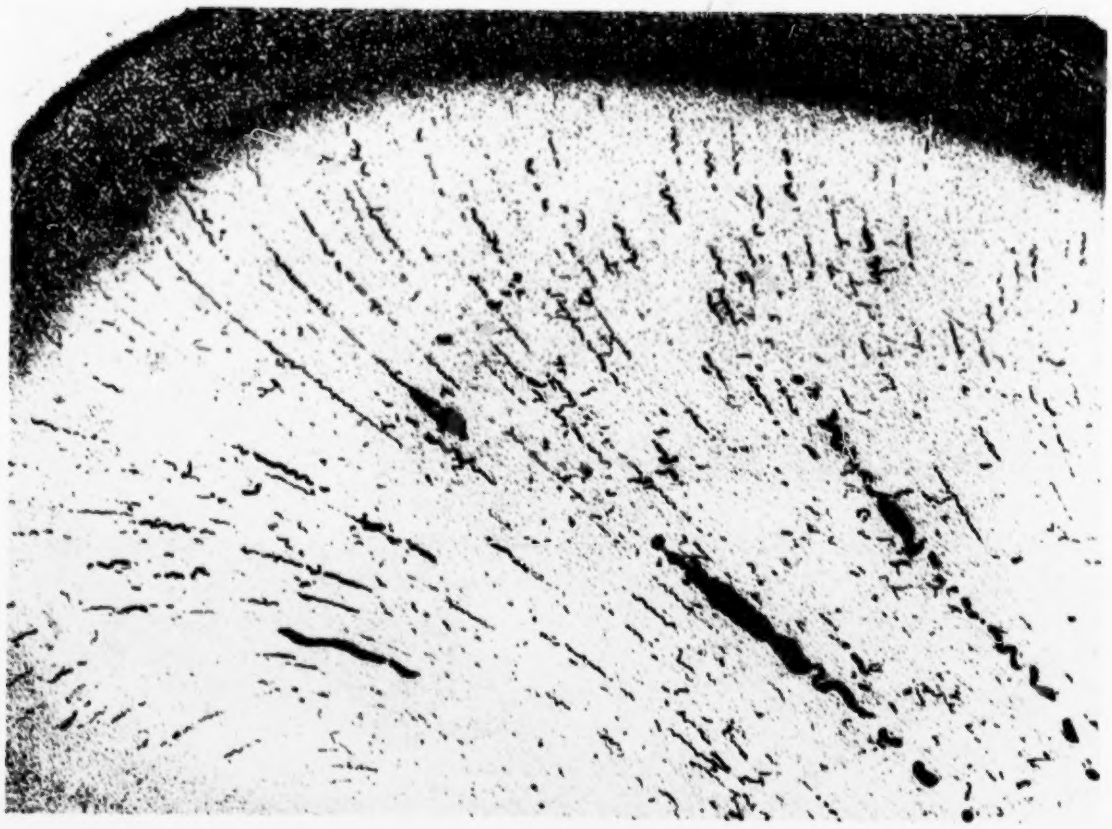


FIGURE 3.—Long radial veins of the corona radiata. Note absence of tangential anastomoses. (From Larroche, 1964, fig. 4 in *Biol. Neonat.* 7: 26–56)

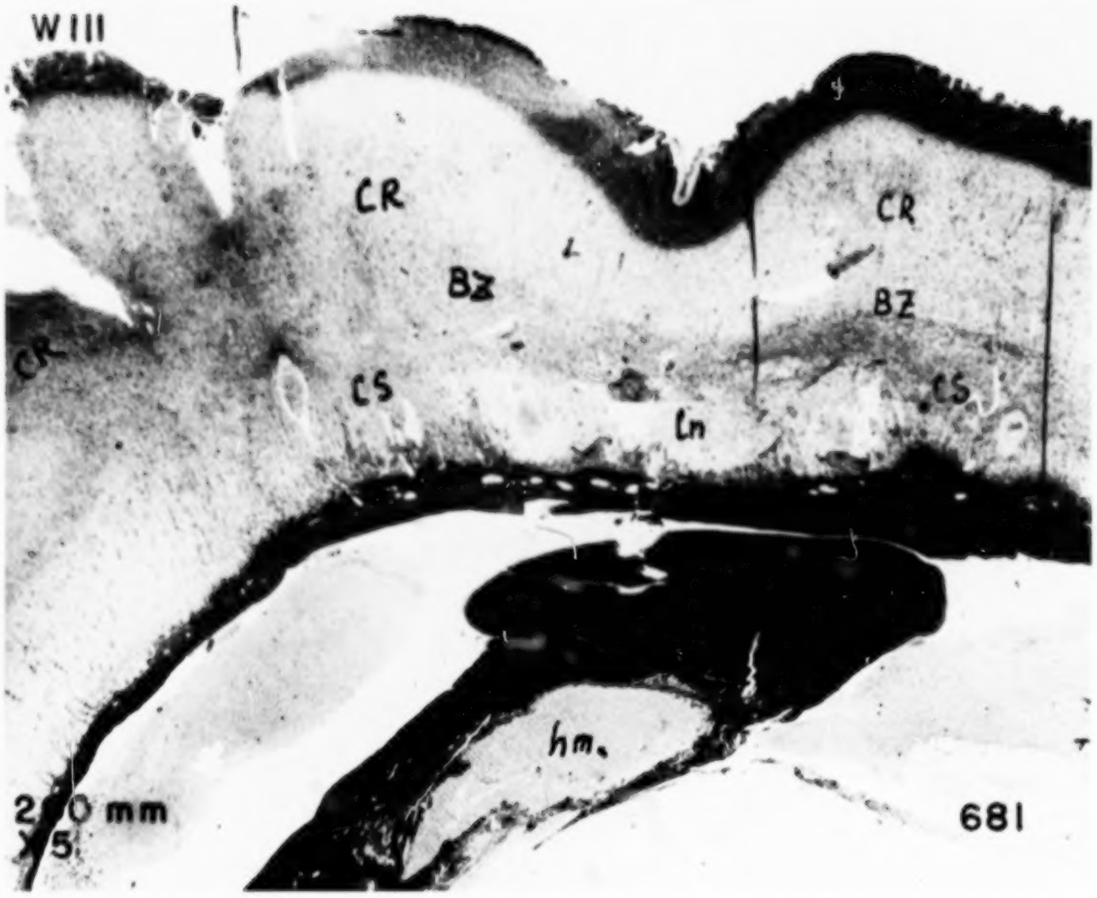


FIGURE 4.—"Gross hemorrhage" (*hm*) in the matrix of the ganglionic eminence in a stillborn at 24 fetal weeks. Note extensive liquefaction necrosis (*ln*) of the centrum semiovale (*CS*), limited sharply by the architectonic demarcation zone (*BZ*) and sparing the corona radiata (*CR*) (Cf. the converse in fig. 5a)

the border zone of fibroarchitectonic demarcation between the centrum semiovale and the corona radiata (fig. 4). It is a notable fact that small foci of leucomalacias ("white spots") described by Banker and Larroche in moribund neonates occur in this deep ("periventricular") zone. Conversely, infarcts and hemorrhages in the cortical plate and corona radiata are exceptional in stillborn prematures under 36 fetal weeks; they become common in this superficial zone and often spare completely the centrum semiovale in term infants, particularly those with histories of birth trauma. This is illustrated in our fig. 5a, and even more explicitly in Dr. Kemper's paper (see his fig. 5b) in this symposium.

In this connection, it appeared of interest to inquire as to the frequency of occurrence, degree of severity, and topographic distribution of the terminal hemorrhagic extravasates in the brain wall in the stillborn premature and nonviable neonates.

Method

Standard, whole-brain serial sections of 226 autopsy specimens were studied. Hemorrhagic extravasates in the brain wall were classified as follows:

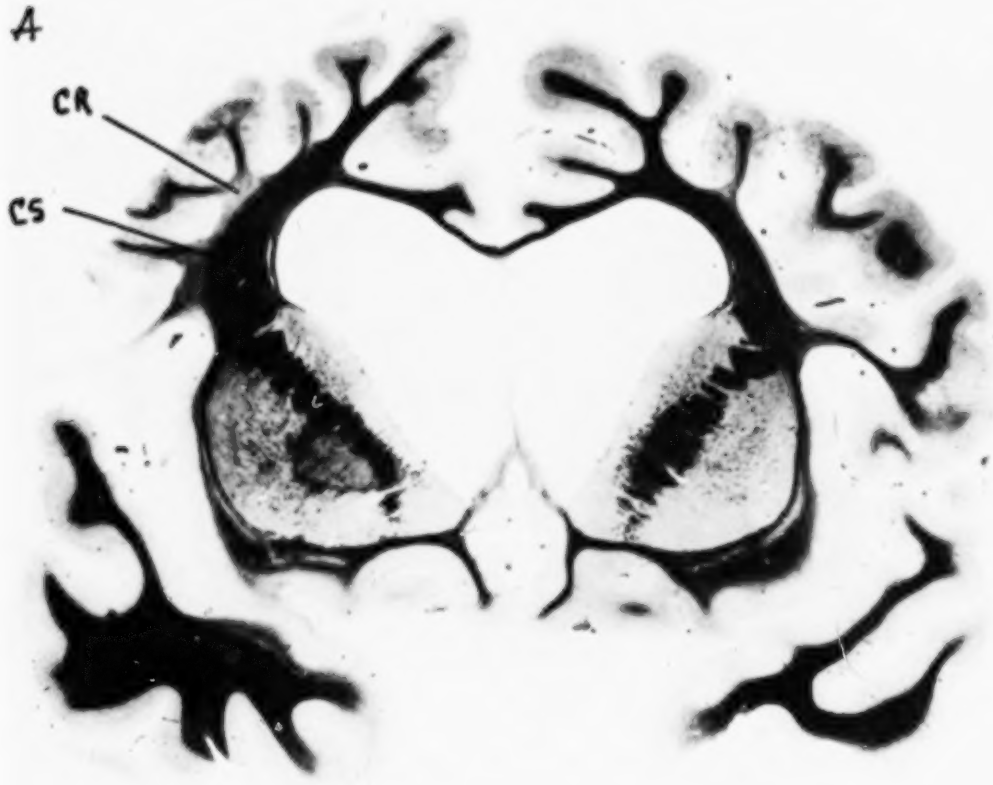


FIGURE 5-*a*.

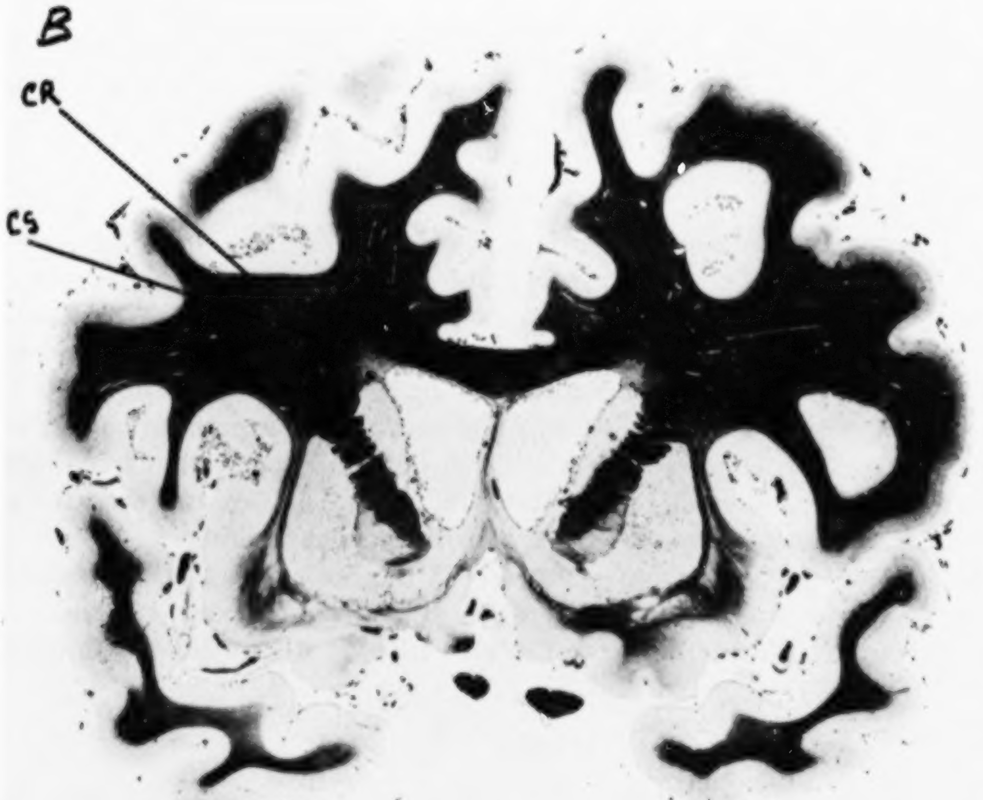


FIGURE 5-*b*.

FIGURE 5.—*a*: Granular atrophy of the cortex, with severe atrophy of the corona radiata (*CR*) and of corpus callosum, and preservation of the projection fibers in the centrum semiovale (*CS*) in a 52-year-old mentally retarded male with history of "difficult birth." (See also fig. 5b in Dr. Kemper's paper in this symposium) *b:* Normative anatomical control section in the same plane and at the same level of the hemispheres as in a, from the brain of a 67-year-old competent housewife who was in good health, until death of a coronary occlusion. Note that in a, as compared to b, the width of the brain wall between the lateral ventricles and cortical plate is reduced almost entirely at the expense of the width of the corona radiata.

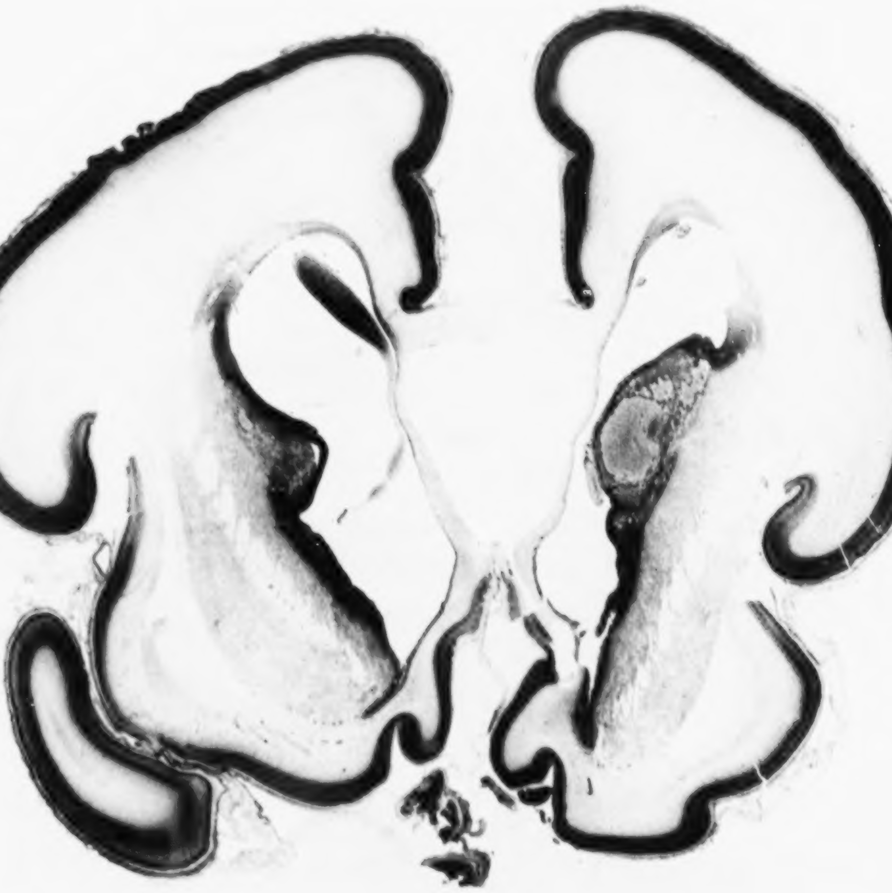


FIGURE 6.—"Gross hemorrhage" in the ganglionic eminence.

Blood extravasates recognizable as such on simple inspection of transluminated slides, classified as *gross hemorrhages* (fig. 6) ;

Blood extravasates recognizable under low-power dissecting microscope at 6X magnification, classified as *small hemorrhages;*

Blood extravasates recognizable only under 3.5 mm objective of a compound microscope, classified as *simple extravasates* (fig. 7) .

From every 10th to every 20th section of each whole-brain series of sections were examined. The position and size of extravasates in the brain wall are being

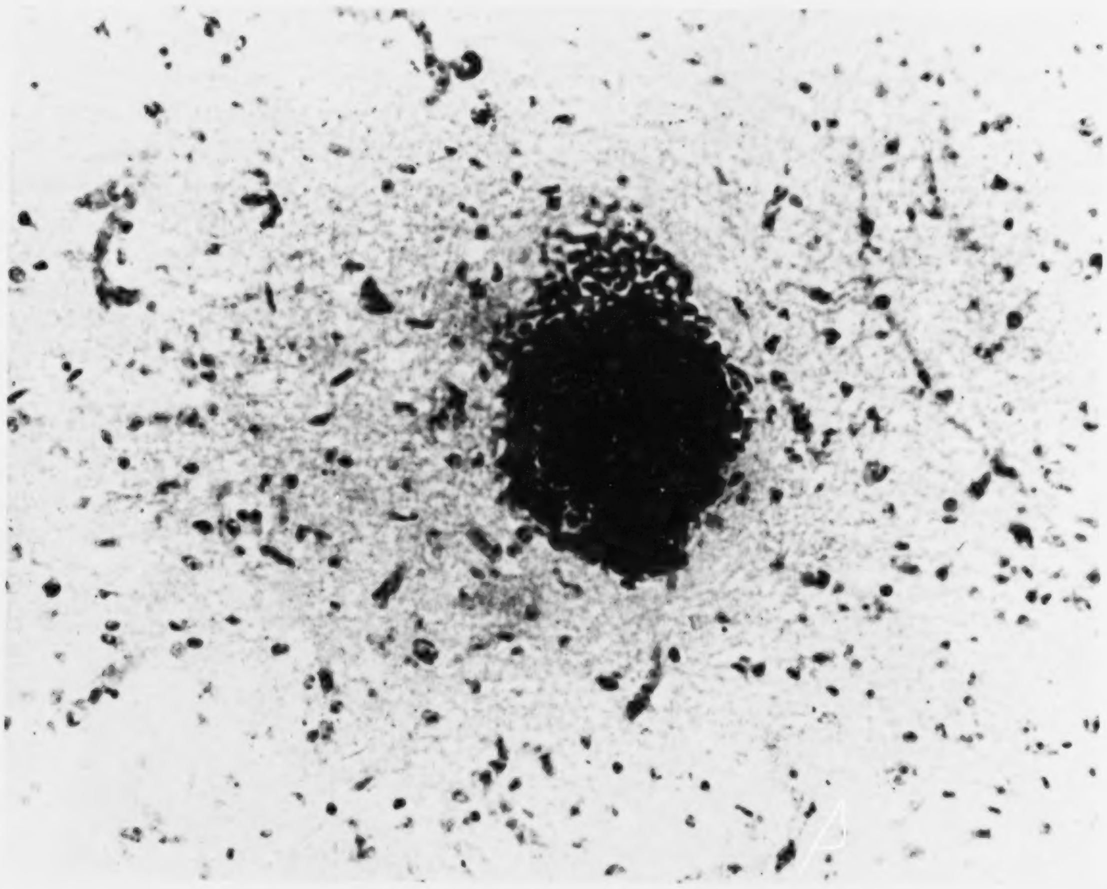


FIGURE 7.—"Simple hemorrhagic extravasate."

plotted. The study of quantitative distribution of extravasates with regard to their site, size, and the fetal age is in progress. The following is a preliminary report of our findings.

Results

Frequency of hemorrhages is shown in Table 1:

TABLE 1.

Simple extravasates only	131	(58%)
Small hemorrhages and simple extravasates.	27	(12%)
Gross and small hemorrhages and simple extravasates.	68	(30%)
TOTAL	226	(100%)

All these hemorrhages arose in the veins. In none of the specimens was there evidence of dural tears, thromboses of sinuses, subdural hematomas or primary subarachnoid hemorrhage.

Topographic distribution in the brain wall. Of the 68 gross-hemorrhaged specimens, 62 had hemorrhages in the certrum semiovale; 35 of these arose in the matrix layer. In only six specimens (2.6 percent of the group) were they located in the superficial zone (corona radiata) of the brain wall.

The small hemorrhages showed a wider distribution in the brain wall. They were most frequent in the matrix layer and in the deep zone and least frequent in the superficial zone.

The simple hemorrhagic extravasates were present in the brain wall of all 226 specimens without exception, and showed the least discrete predilection for the deep zone.

Fetal age and location of hemorrhages in the brain wall. Of the 116 specimens in the fetal age-range from fifth to seventh lunar month, gross hemorrhages occurred in 52 (44 percent). Of the 110 specimens in the age-range from the eighth lunar month to term, gross hemorrhage showed in only 16 specimens (14.5 percent of this older age group).

The gross hemorrhages in the younger age group were all in the deep zone; 31 (59.6 percent) were in the matrix layer. In the 16 specimens of the older group, gross hemorrhages were present in the deep zone in 10 (62.5 percent); in the other six they were located in the corona radiata and cortical plate. Table 2 gives the distribution of the gross hemorrhages by age and location in the two architectonic zones of the brain wall.

TABLE 2.

LOCATION OF GROSS HAEMORRHAGES IN THE BRAIN WALL WITH REGARD TO FETAL AGE IN 68 STILLBORN AND NON-VIABLE NEONATES

FETAL AGE	NO. OF CASES	LOCATION IN THE BRAIN WALL	
		CENTRUM SEMIOVALE	CORONA RADIATA
5th Month	16	16	0
6th Month	18	18	0
7th Month	18	18	0
8th Month	8	6	2
9th Month	5	3	2
10th Month	3	1	2
TOTALS:	68	62	6

Table 3 gives the location of small and gross, single- and multiple-site hemorrhages in the periventricular matrix of 134 specimens. Single-site periventricular hemorrhages occurred in 65. In two specimens the hemorrhages were in the wall of the frontal; in three, the occipital; and in two, the temporal horns of the lateral ventricles. In 58 specimens (90 percent) they were located in the ganglionic eminence at the level of the foramen of Monro. Of 69 multiple-site hemorrhage specimens, 24 had hemorrhages at the level of the foramen of Monro and cella media; 21 in the walls of the frontal; 12 in the occipital; and 12 in the temporal horns.

TABLE 3.

LOCATION OF SINGLE-SITE AND OF MULTIPLE-SITE HEMORRHAGES IN THE MATRIX LAYER

LOCATION	SINGLE SITE	MULTIPLE SITE	TOTALS
Foramen of Monro	58 specimens	24 specimens	82 specimens
Frontal Horns	2 "	21 "	23 "
Occipital Horns	3 "	12 "	15 "
Temporal Horns	2 "	12 "	14 "
TOTALS	65 specimens	69 specimens	134 specimens

DISCUSSION

Terminal hemorrhages in the brain wall of stillborn premature and nonviable neonates who die soon after birth are common autopsy findings (Larroche). They are generally attributed to failure of circulation and are of little interest to either the pathologist or the clinician.

Nevertheless, they are meaningful as indices of the differential, age-linked vulnerability of the two histogenetically and architectonically different zones of the brain wall to the effects of circulatory failure at different stages of brain development. We shall discuss these hemorrhages in the context of the topographic anatomy and development of these zones of the brain wall.

Rückensteiner and Zöllner, Grunewald, and more recently, Larroche showed that these terminal hemorrhages occur most frequently in the periventricular matrix and are associated with stasis and sometimes thrombosis of the deep cerebral veins. They may be associated with massive intraventricular hemorrhages which may extend from the ventricles into the subarachnoid spaces (Larroche). Our results fully confirm these observations. As pointed out by Larroche, the most vulnerable area is near the foramen of Monro where the periventricular tributaries from the corpora striata and centrum semiovale to the paired internal cerebral veins change the direction of flow at a sharp angle into the median vein of Galen. The results presented in Table 3 support this mechanical interpretation.

The results of our survey presented in Table 2 indicate that, up to the eighth month of fetal life, there is a gradient in the frequency and severity of brain hemorrhages reaching its height in the matrix and deep zone of the brain wall, i.e., in the ganglionic eminence and centrum semiovale, and decreasing toward the corona radiata and cortical plate. However, from the eighth month to term there is an apparent inversion of this gradient, corresponding to the great acceleration in the tempo of growth in mass and development of the superficial zone of the brain wall, i.e. of the cortical plate and of the corona radiata.

The deep zone grows and differentiates most rapidly from the fifth to the eighth fetal month. After the eighth month the corpora striata and centrum semiovale begin to lag in growth as compared to the rapid expansion of the cortical plate and increasing width of the corona radiata, growing at the expense of the juxtaventricular zone of the brain wall and periventricular matrix, which becomes nearly exhausted at term.

An entirely different and much wider spectrum of factors comes into play in the hemorrhages, thromboses, and encephalomalacias occurring in the brain wall of fetuses and neonates near term and after birth. The increased demand on the blood supply by the rapidly developing cortical plate and white matter of the corona radiata is only one, more general, of these factors. Because of its sheer bulk and external position, the superficial zone of the brain wall becomes vulnerable to the effects of pressure and mechanical trauma to the head and neck at birth. Near term, not only circulatory failure with its corollaries of stasis and thrombosis of the deep cerebral veins but also *arterial* cerebral infarcts (unknown before the eighth fetal month [Manterola, *et al*]) begin to occur. Those in the superficial zone of the brain wall are compatible with a long postnatal survival. The encephalomalacic lesions occurring in the superficial zone (corona radiata), such as granular atrophy of the cerebral cortex (ulegyria) and circumscribed porencephalic defects in the brain wall, sparing the basal ganglia and dense fiber systems of the centrum semiovale, are a common autopsy finding in various clinical modalities of "cerebral palsy" and mental retardation (fig. 5).

Summary and Conclusion

The terminal hemorrhagic extravasates are a constant finding in all premature stillbirths and are venous hemorrhages, small or large. In the stillborn fetuses under the eighth fetal month they occur almost exclusively in the matrix layer and centrum semiovale, and are exceptional in the corona radiata and cortical plate. After the eighth fetal month the deep zone becomes less vulnerable to the circulatory disturbances, while the vulnerability of the superficial zone of the brain wall increases. The two architectonic zones of the brain wall provide the pathologist with a descriptively useful and, probably, pathogenetically important anatomical reference for a survey and study of the perinatal pathology of the brain.

REFERENCES

BANKER, B. Q., and LARROCHE, J. C. Periventricular leukomalacias of infancy. A form of neonatal anoxic encephalopathy. *Arch. Neurol. 7:* 386–410, Nov. 1962.

GRUENWALD, P. Subependymal cerebral hemorrhage in premature infants, and its relation to various injurious influences at birth. *Amer. J. Obstet. Gynec. 61:* 1285–1292, June 1951.

KLOSOVSKII, B. N. *Blood circulation in the brain.* Translated from Russian by Israel Program for Scientific Translations, 1963. National Library of Medicine (Cat. No. TT-63, 11171), Washington, D.C.

LARROCHE, J. C. Hémorragies cérebrales intra-ventriculaires chez le premature. *Biol. Neonat. 7:* 26–56, 1964.

LINDENBERG, R., and SPATZ, H. Uber die Thromboendarteritis obliterans der Hirngefasse (Cerebrale form der v. Winiwarter-Buergerschen Krankheit). *Virch. Arch. Path. Anat. 305:* 531–557, 1939.

MANTEROLA, A., TOWBIN, A., and YAKOVLEV, P. I. Cerebral infarction in the human fetus near term. *J. Neuropath. Exp. Neurol. 25:* 479–488, July 1966.

PADGET, D. H. The development of the cranial venous system in man, from the viewpoint of comparative anatomy. In: *Contributions to Embryology,* Carnegie Institution of Washington, Vol. 36, 1957, pp. 79–140.

RÜCKNER, E., and ZÖLLNER, F. Ueber die Blutung im Gebiete der Vena Terminalis bei Neugeborenen. *Frankfurt Zeitschr. f. Path,* 1929.

SCHLESINGER, B. The venous drainage of the brain, with special reference to Galenic system. *Brain 62:* 274–291, Sept. 1939.

VANDER EECKEN, H. M. *The anastomoses between leptomeningeal arteries of the brain. Their morphological, pathological and clinical significance.* Charles C Thomas, Springfield, Ill., 1959.

POSTMORTEM NEUROPATHOLOGIC FINDINGS IN PATIENTS WITH "BIRTH INJURY"

THOMAS L. KEMPER, M.D.
Department of Neurology
Harvard Medical School
Boston, Massachusetts

Among 260 consecutive autopsies performed by Dr. Clemens E. Benda at the W. E. Fernald State School during a period of 15 years (1947–1961), there were found in his collection 33 cases which were processed histologically and were used in this study. The ages at autopsy ranged from 4 months to 40 years. Twenty-five of these cases were diagnosed *clinically* as "birth injury." An attempt was made to correlate the clinical histories with the histopathological findings in these cases.

On the basis of this study the 33 cases fell into six groups:

1. Malformations	4 cases
2. Kernicterus	5 cases
3. Status marmoratus	6 cases
4. Primary infarction of thalamus	3 cases
5. Cerebral infarction without status marmoratus	8 cases
6. Miscellaneous	7 cases

1. *Malformations.* There were four cases which clinically were diagnosed as birth injuries. All four cases showed either gross or architectonic evidence of disturbed maturation of the brain such as shown in fig. 1. In none was there histopathologic evidence of destructive, traumatic, vascular, or old degenerative lesions.

2. *Kernicterus.* There were five cases with histopathological lesions characteristic of kernicterus. Clinically, in one case the history was unknown, three cases were diagnosed as birth injuries, and only one as kernicterus. All five cases showed severe cell loss in the inner division of the globus pallidus and subthalamic nucleus (fig. 2). Of the four cases clinically not recognized as kernicterus, one had a history of postnatal jaundice, which led to a "spastic state" within 2 weeks; one was said to have been born "black and blue" and needed a transfusion at 3 days of life; and one was premature and kept in an incubator for 3 to 4 weeks.

3. *Status Marmoratus.* There were six cases with the characteristic lesions of the so-called "status marmoratus," four diagnosed clinically as birth injuries. All these cases showed characteristic marbling of the striatum and irregular cell loss in the thalamus. In 3 of 4 cases in which sufficient material was available, a cell loss was found also in the Ammon's horn.

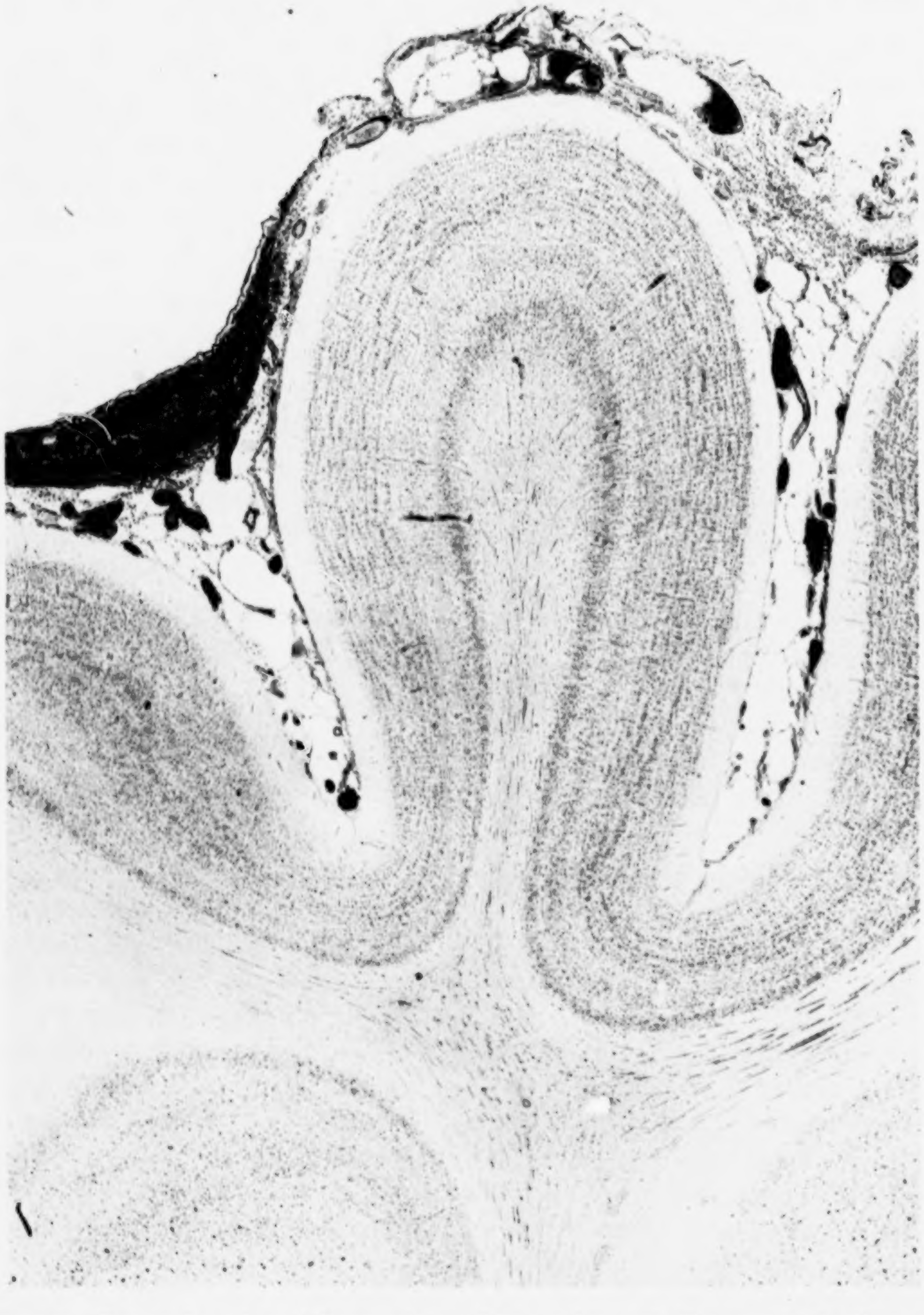


FIGURE 1.—Example of architectonic malformation of the cortical plate in a 7-year-old mentally retarded child showing poor lamination and persistence of "ripple pattern" of nerve cell distribution in layers 2 to 4 of the cortical plate.

Cortical infarctions were observed in 4 of the 6 cases. In two of these the infarcts were characteristically in the so-called "border zones" of distribution of the arterial supply, and were maximal in the parietal-occipital region. The infarcted zones showed an obliterative arteriopathy with stagnation thrombosis and

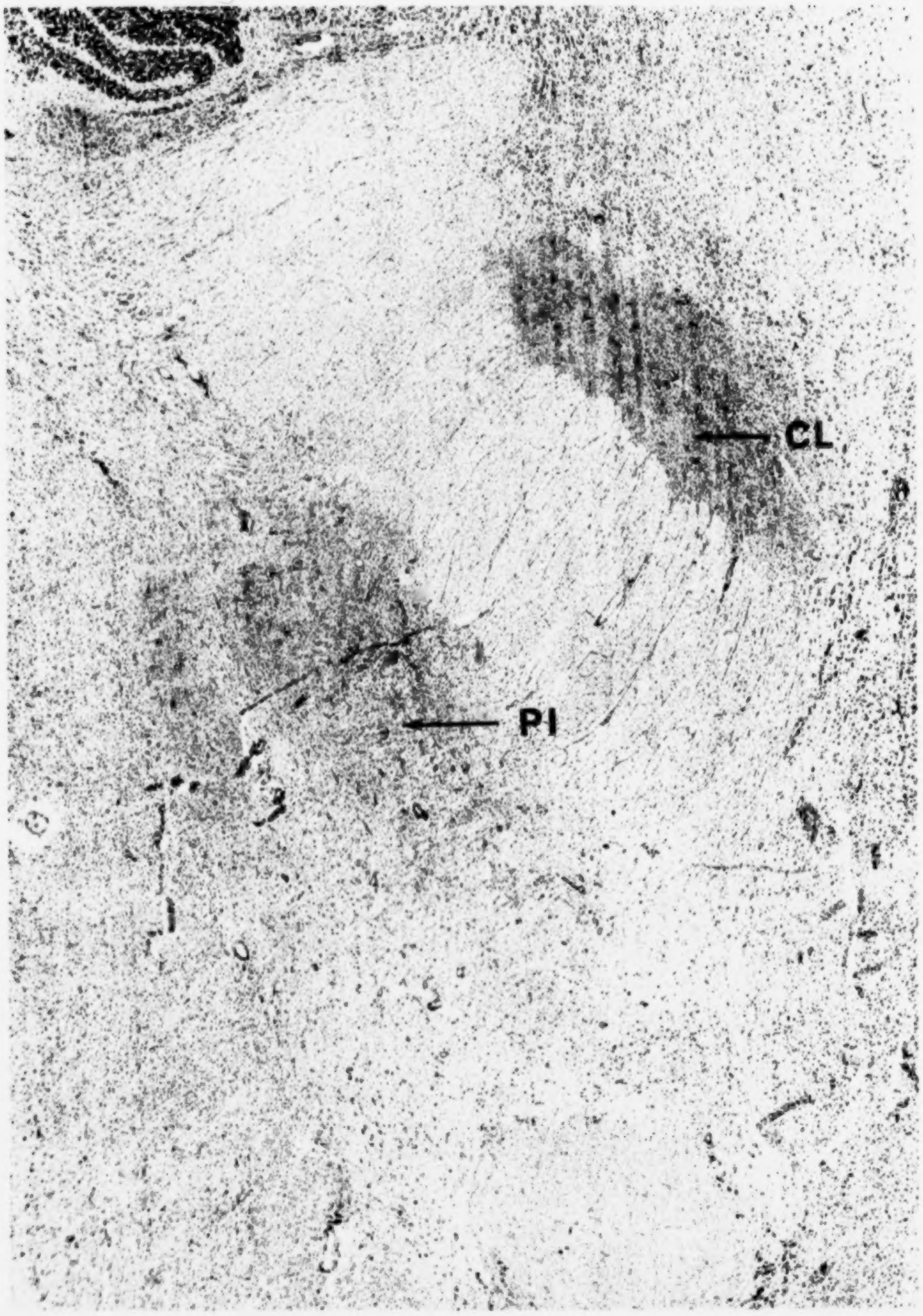


FIGURE 2.—Example of kernicterus in a 4-month-old infant with jaundice since birth. Note cell loss and gliosis in subthalamic nucleus (*CL*) and inner division of the globus pallidus (*PI*).

recanalisation of the pial arteries ,fig. 3) . One case was remarkable in that it was the only case in the entire series studied in which extensive laminar necrosis of the cortex was found. The pial arteries were normal in this case and the distribution pattern of the infarction was not in the "border zones." One case had bilateral subdural membranes indicative of old subdural hematomas.

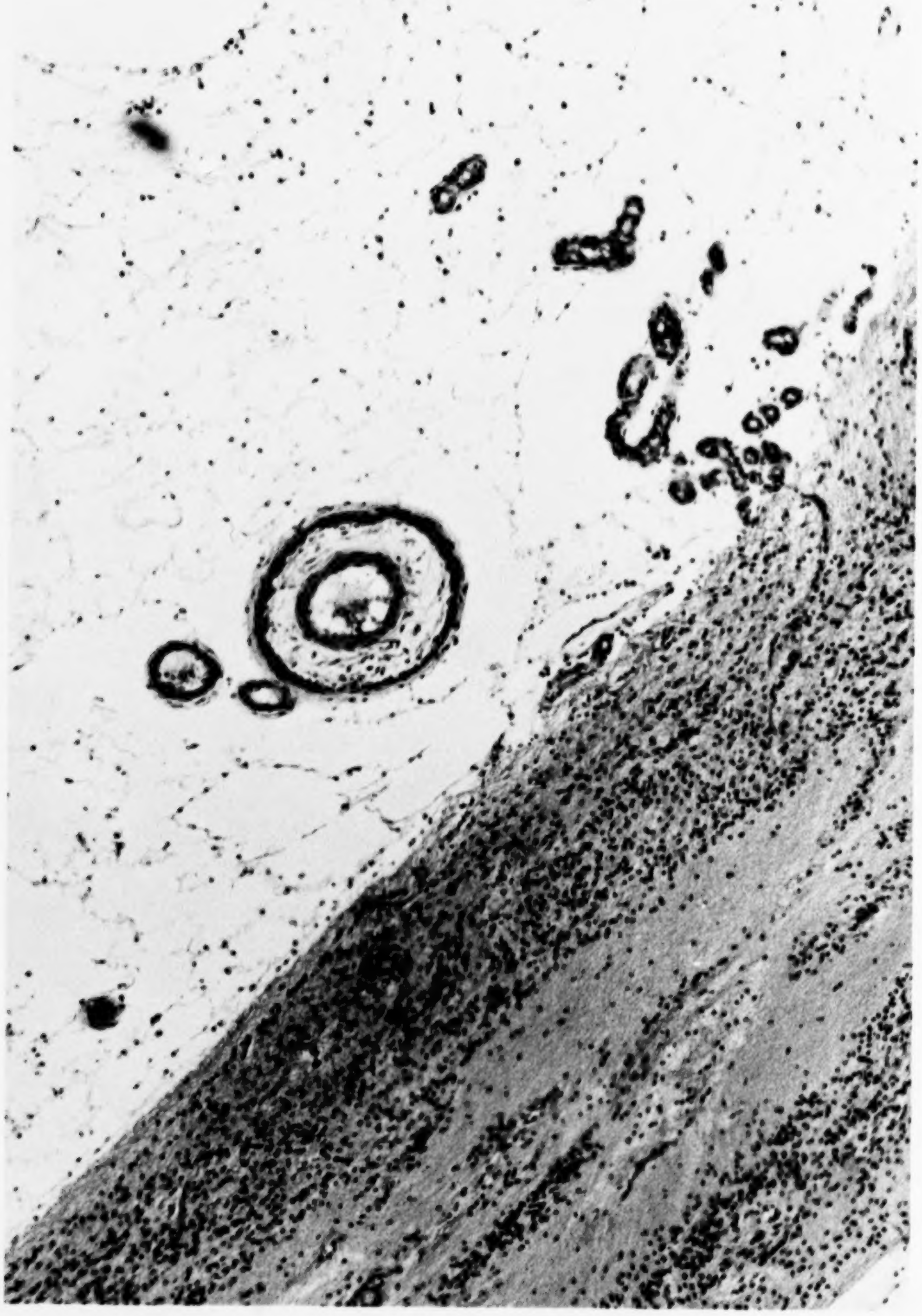


FIGURE 3.—Recanalisation of a pial artery in the zone of old cortical infarction in a case with status marmoratus of the striatum.

In 1 of the 6 cases, the gestational age at birth was not known; the other five cases were term births. One of these was said to have had "asphyxia"; the umbilical cord was "wrapped around the neck." The other four cases either required "resuscitation" or were said to have been "given up for dead."

4. *Primary Infarction of Thalamus.* There were three cases in which patchy infarction of thalamus was found (fig. 4), without lesions (either cortical or

striatal) elsewhere in the forebrain. Ammon's horn was intact in all. In 1 of these 3 cases there was infarction of the cerebellar cortex. In 2 of the 3 cases the clinical history was unknown. One case was clinically diagnosed as birth injury.

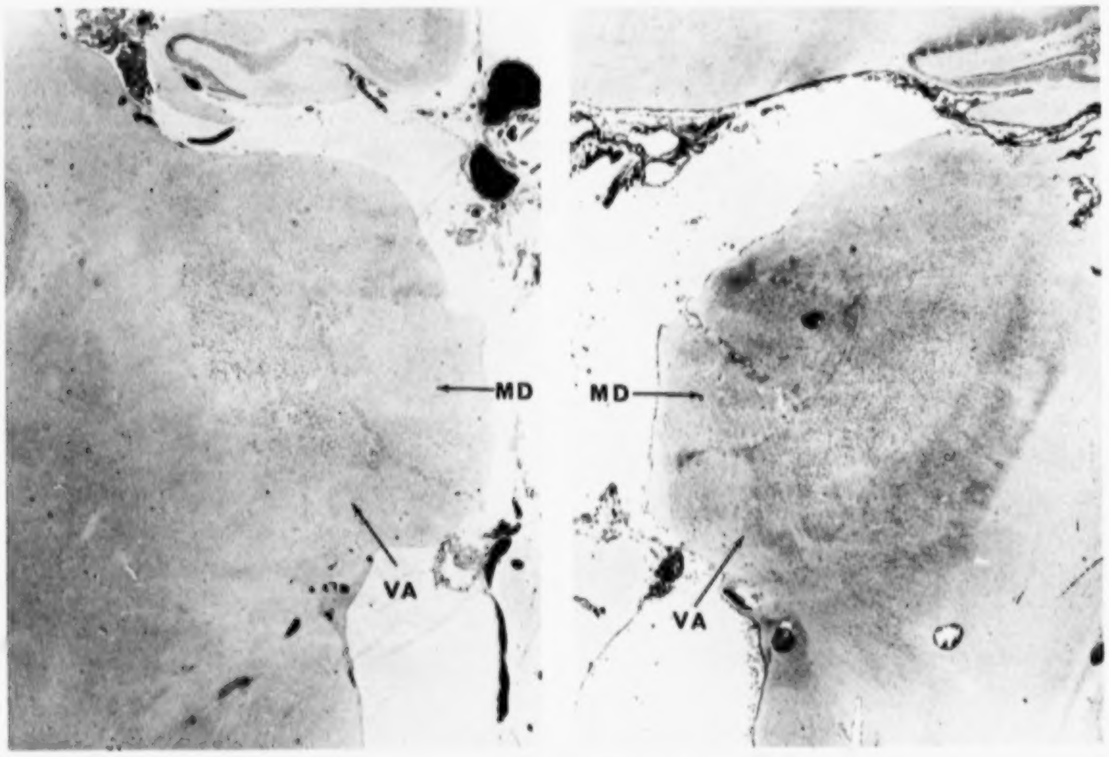


FIGURE 4.—a: Primary infarction of thalamus in a 37-year-old mentally retarded male with congenital spastic diplegia. Note extensive cell loss in the medial dorsal (*MD*) and ventral anterior (*VA*) nuclei.

b: Normative control section of thalamus in the same plane and at the same level as in (a) from a 57-year-old woman who died of "endocarditis."

5. *Cerebral Infarction without Status Marmoratus.* (Fig. 5a and b). There were eight cases of cerebral infarction without status marmoratus. Clinically six of these were diagnosed as birth injury. In 3 of these 8 cases the infarctions were extensive and the brain weights ranged from 200 to 365 grams. In five cases the infarctions were less extensive and were maximal on the convexity of the parietal-occipital region where both the cortex and a variable amount of subcortical white matter were destroyed. Smaller foci of cortical infarction were found on the medial aspect of the hemispheres and in the region of the insula and opercula. In 1 of these 5 cases the infarcts were in the border zones between the anterior, middle, and posterior cerebral arteries. In the other four cases the topography of the infarction could not be determined with reference to the "border zones" because of insufficient material. Sections of Ammon's horn were available in four cases and all were found normal. Cerebellar lesions were found in 4 of the 5 cases in which sufficient material was available. Bilateral subdural membranes were found in one case.

In this group of eight cases no clinical information was available in two cases. The review of the birth records of the six other cases revealed that 3 were

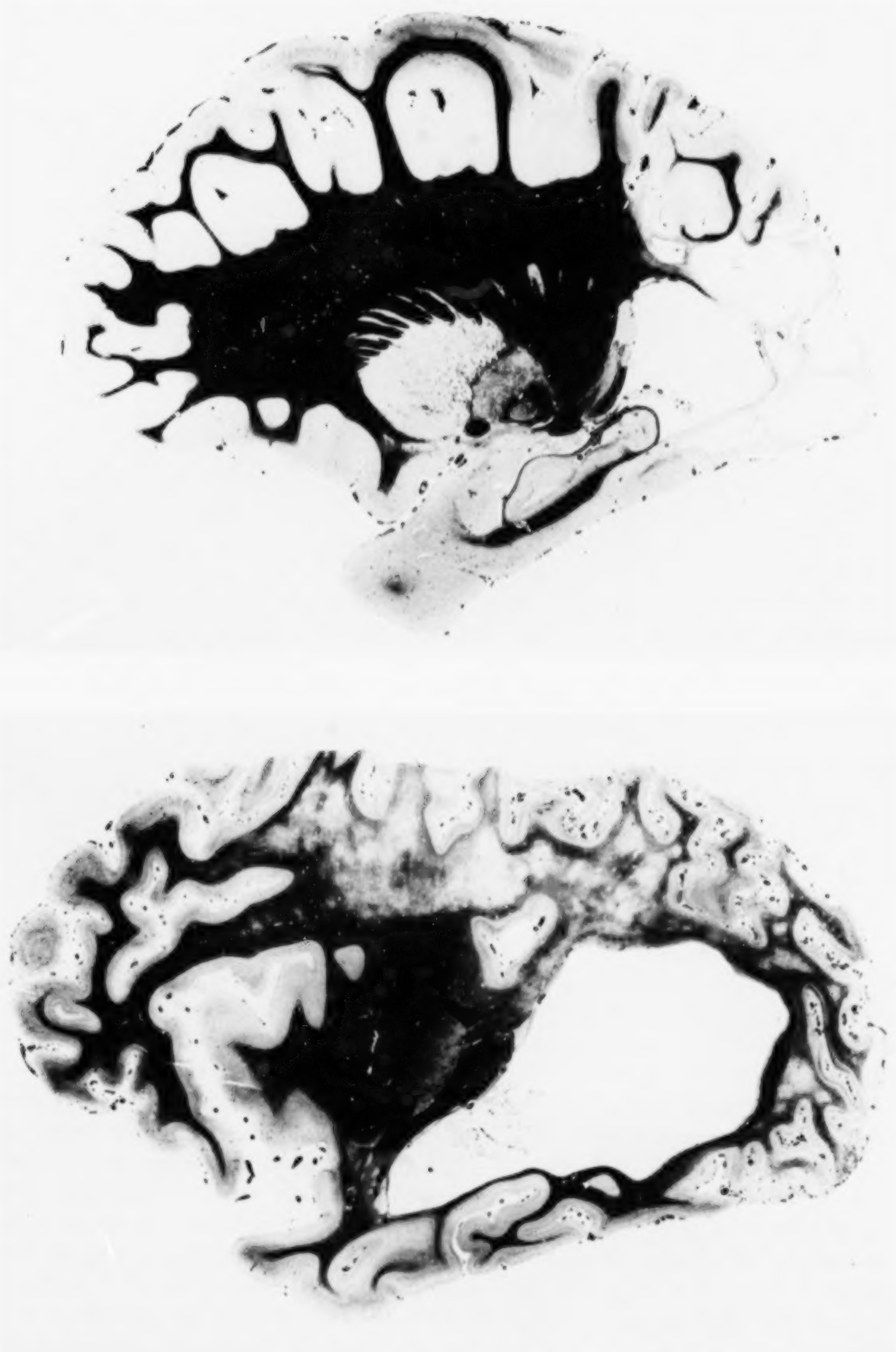


Figure. 5.—a: Old cystic infarction of the occipital lobes in a 6-year-old microcephalic, severely retarded epileptic child delivered by high forceps.

b: Extensive cortical infarction in a 6-year-old severely retarded child delivered at term by caesarian section after 12 hours of labor. Note the infarct is limited to the cortex and white matter of the corona radiata and spares the structures of the centrum semiovale (see this symposium: Yakovlev and Rosales, their figure 5a and discussion).

term deliveries, 2 were postmature (1 week and 6 weeks) and 1 was premature. Three of these 6 cases were delivered by high forceps, one of these because of amniotic fluid staining. In two other cases the delivery was said to be "instrumental," one of these because of maternal eclampsia with seizures and the other because it was a large 14-pound baby. One case was delivered by caesarian section after 12 hours of labor and passage of meconium.

Information as to the status of the infants immediately after birth was available for five of these cases and all were abnormal. Two were described merely as being "peculiar"; one was cyanotic and had seizures soon after birth; one required oxygen administration and had seizures after birth; one was unresponsive with "breathing difficulties" and minor seizures."

6. *Miscellaneous.* There were seven cases placed tentatively in a miscellaneous group; all were diagnosed clinically as birth injury. Five of these 7 cases showed neither evidence of malformation nor of any destructive lesions in the brain. In 3 of these 5 cases the birth was recorded as abnormal. In two cases cerebral lesions were found; one with a history of a maternal "viral infection" in the 8th month of pregnancy showed widespread lesions located mainly in the upper brain stem. The other case was a 4-year-old child who died of bronchopneumonia with seizures and showed severe and widespread agonal changes in the brain which made his histopathological diagnosis uncertain.

Comment and Summary

The clinical diagnosis of "birth injury" in these cases is ambiguous. If one means by the term "mechanical injury," evidence of it was noted in only two (subdural hematonas) of the 33 cases. If the term is intended to refer to a catastrophic hypoxic or ischemic disorder of the brain incident to birth, it was inaccurate in half of the cases (four developmental malformations in group 1, five cases of kernicterus in group 2, one case of probable viral infection, and six of undetermined type in group 6).

The groups of cases with focal destructive lesions in the cortex, striatum, thalamus, Ammon's horn, and cerebellum (groups 3 and 5) fall into two catgories, one with status marmoratus with histories of grave difficulties in resuscitation at birth in nearly all instances, the other with destructive cortical and subcortical lesions without status marmoratus, and abnormalities of labor but without history of difficulties in initiating breathing. In properly examined cases the cortical infarctions in both these categories were found to be maximal in the border zones between the major cerebral arteries. The recanalized arteries found within the infarcts were of the type that we have called stagnation-thrombosis. In these two groups, particularly the former, changes were also present in the cerebellum and Ammon's horn. Primary infarction of the thalamus as a pathological entity was observed in cases in both groups and occurred without cortical lesions. Almost all these cases were term deliveries.

The obvious interpretation of the lesions is that they are produced by hypoxia and impairment of blood flow and not by trauma *per se,* a view in harmony with that of most neuropathologists. There were no lesions that could be the residue of matrix hemorrhages or terminal vein thrombosis. The clinical data on the two cases with subdural membranes provided no clue as to the occurence of trauma, either at the time of birth or later. When the entire collection was reviewed in the manner indicated, the virtual absence of prematurely born infants is noteworthy (only two cases found).

EPIDEMIOLOGIC STUDIES OF HEAD INJURY

William Caveness, M.D.
National Instiute of Neurological Diseases and Stroke
Bethesda, Maryland

Accidental death and disability in our time has achieved a magnitude comparable to the plagues of the Middle Ages. In the U.S. in 1966, accidents were the fourth cause of death, following heart diseases, cancer, and stroke, and the leading cause of death from ages one to 44. But it is among the survivors that the ranks of the disabled appear.

The National Center for Health Statistics surveys of accidental injuries from July 1965 to June 1967 indicate an annual toll of 48,483,000 persons suffering 51,243,000 injuries. An injured person is defined as anyone who is medically attended and/or whose activity is limited for at least one full day. One-seventh of all accidental injuries occur in infants and children below the age of six. This amounts to 7.25 million children injured in the U.S. each year.

Our concern here is the craniocerebral trauma or injuries that may result in brain damage with recognizable sequelae. Since definitive information regarding the incidence of such injuries does not exist, I have chosen to present only that data which can be accepted with reasonable confidence.

One source of information is a National Center for Health Statistics survey of 134,000 persons in 42,000 households interviewed from July 1966 through June 1967. The report deals with the incidence of head injuries as defined by the World Health Organization's International Classification of Diseases. These are limited to skull fractures, open scalp wounds, contusion or hematoma of scalp, concussion, cerebral laceration and contusion, subarachnoid, subdural, and extradual hemorrhage following injury, other intracranial hemorrhage, and head injury of other types including brain injury, cerebral irritation, traudelirium or stupor, crushing of head, and open wounds of head not otherwise specified.

These injuries were found to have occurred in approximately 3,053,000 instances, of which 794,000 or 26 percent occurred in children under six years of age. Of the 1,375,000 head injuries sustained in the home, 614,000 or 44.7 percent occurred in this age group. Motor vehicle or other accidents outside the home were responsible for 180,000 head injuries in children under six. From these surveys, the annual incidence of significant head injuries in infants and young children may be conservatively estimated at 794,000 or 3.3 percent of the population under six years of age (24,046,000).

Another perspective is afforded by the study of 3,440 injured children ages one through 14 who were admitted to the emergency room of a Columbus, Ohio, general hospital in 1961 (Zollinger). Injuries to boys outnumbered those to girls two to one, except in the first year of life. The peak incidence for both sexes was in the second year of life and remained near this level through the preschool years. Most injuries occurred in the spring and summer. Eighty-six percent occurred between noon and midnight and most between 5 and 8 p.m.

Falls caused 46 percent of the accidents, broken glass and sharp objects 16 percent, automobiles and bicycles 9 percent and sports and other activities 11 percent. The head was the most commonly injured part of the body, accounting for 41 percent of the total injuries.

Changing Concepts in Epidemiology. Alexander Langmuir, Chief, Epidemiology Program, National Communicable Disease Center, Atlanta, defines epidemiology as the study of the occurrence of disease in populations. This includes not only the determination, but the interpretation of incidence rates of disease. By relating the rates to time, to place, and to persons, patterns evolve that permit predictions of future trends.

Over the past several decades, such surveillance has made spectacular contributions to the management of smallpox, malaria, poliomyelitis, and other infectious and/or communicable diseases. Outside this realm of biological hazards, these techniques have been employed for only a few years and to a far less extent.

William Haddon, Director, National Highway Safety Bureau, Department of Transportation, is amongst those with an increasing awareness of the relationship between man and his environment, of human ecology, especially of man's relationship with certain potentially hazardous physical attributes of his society. There has been a shift from descriptive accounts of accidental injuries to categorization in etiological terms. This, of course, is a prerequisite for proper control. In his approach to traffic accidents, Dr. Haddon stresses the importance of pre-injury, injury, and post-injury factors in the host and the environment.

Mental Retardation. The place of trauma as an etiological agent in mental retardation has not been precisely defined. In the literature, postnatal trauma has been accorded a very small place as an etiological factor. G. G. Hinton in a study of 1,137 retarded children found 129 or 11.3 percent in whom retardation was first noted after a specific postnatal event. Herman Yannel in a study of 1,137 admissions to a training school in Southbury, Connecticut, attributed 1.4 percent to postnatal injury. Chester A. Swinyard, in a study of 1,283 children with cerebral palsy referred to the Institute of Physical Medicine and Rehabilitation in New York, found that 143 or 11 percent acquired the deficit after an apparently normal gestation and neonatal period. Twenty-five or 1.9 percent of these were related to trauma.

Design of a Study That Would More Accurately Determine the Place of Postneonatal Trauma in Mental Retardation. From the preceding, several things are apparent:

(1) Craniocerebral trauma is and is likely to remain a part of our way of life for the foreseeable future.

(2) Such trauma is occurring in at least 3.3 per cent of infants and young children whose central nervous system is still in a phase of rapid development. Raymond Adams has pointed out the extraordinary susceptibility of the child's nervous system to a large array of patho-physiological events. Among other derangements the immature nervous system is not able to effectively regulate water and salt metabolism or temperature control under conditions of infection and injury. Knox Finley has clearly established the relation between sequelae

from Western equine encephalitis and the age at which the infection was acquired: the younger the infant the greater the liability. Further, he has demonstrated that there may be a delay of several months to several years before the impairment in mental development becomes apparent. The increased vulnerability of the central nervous system to physical trauma with immaturity has been noted by many, and I am sure will be given sharper definition by Dr. Perry Black in his presentation later in this conference.

(3) The relation between mental retardation and postnatal trauma has been sparsely recorded in the literature. As an etiological factor, it is accorded a place of less than 2 percent. Is this really true, or are we making inadequate observations and drawing incomplete conclusions? A more accurate determination of the role of postnatal craniocerebral trauma in the production of mental retardation would require considerable skill in a variety of disciplines, time, effort, and money.

A provisional plan: First, there is required a more adequate appraisal of the over-all incidence and nature of head injuries. A way of obtaining this would be a prospective study including both house-to-house interviews and in-hospital studies in a circumscribed area over a specified period of time.

For elucidation of the problem at hand, special attention would be directed to those under five years of age and, particularly, to those under two years of age at the time of injury. The pre-injury condition of the child will be of importance regarding such factors as nutrition. The increased susceptibility to mental retardation when infection and malnutrition are combined is known, from the work of Herbert Birch, and it is reasonable to suspect a similar relationship between trauma and malnutrition. In the latter, there would be an expected delay in wound healing and the heightened possibility of posttraumatic infection.

In the injury itself, the transfer of energy in excess of threshold will depend on the mechanism or agent of injury and the degree of development in the child. A trivial fall may rupture thin walled, poorly supported veins in a young infant, while an older child may successfully withstand a vehicular accident. In the post-injury phase, the means for recognition of severity, transportation, and proper care will vary with the environment and may be of considerable significance.

Coupled with the determination of the relevant facts from the acute phase of injury, there would have to be a planned follow-up study that would cover a period of not less than five years, and optimally, ten years. At the time of the follow-up studies, there should be not only the routine psychological and neurological evaluations, but selected studies in perception, integration, and memory, as those developed by Dr. Hans-Lukas Teuber. Impairment in central auditory and vestibular function, as well as alterations in cerebral blood flow, should be detected by the methods being developed by Dr. Raymond Adams and his group. These would provide a link between the trauma and impairment in brain function that might otherwise be missed.

Postmortem examinations should be conducted on all in the study population that die during the period of observation.

When all this is done there will be available meaningful information from a single area. For a nationwide appraisal, duplication in six to eight localities would be necessary.

Conclusion. Faced with a task such as this, one has to carefully estimate the yield and make hard choices between the demands within this field of interest. The arguments for this effort that, to me, seem compelling are (1) the existence of trauma as a part of our environment, (2) the immaturity of the brains at risk, and (3) the lack of recognized etiological factors in three fourths of the cases of mental retardation.

REFERENCES

ADAMS, R. D., and SALAM, M. Z. Neuropathologic mechanisms in infectious diseases that relate to mental retardation. In: *The Prevention of Mental Retardation Through Control of Infectious Diseases, NICHD.* Government Printing Office, Washington, D.C., 1968, pp. 187–206.

BIRCH, H. G., and CRAVIOTO, J. Infection, nutrition and environment in mental development. In: *The Prevention of Mental Retardation Through Control of Infectious Diseases, NICHD* Government Printing Office, Washington, D.C., 1968, pp. 227–248.

FINLEY, K. H. Postnatally acquired infections leading to mental subnormality. In: *The Prevention of Mental Retardation Through Control of Infectious Diseases, NICHD.* Government Printing Office, Washington, D.C., 1968, pp. 101–134.

HADDON, W., JR. The changing approach to the epidemiology, prevention, and amelioration of trauma: the transition to approaches etiologically rather than descriptively based. *Amer. J. Public Health 58:* 1431–1438, Aug. 1968.

HINTON, G. G. Postnatal organic causes of mental retardation. *Canad. Med. Ass. J. 87:* 501–507, Sept. 1, 1962.

LANGMUIR, A. D. The surveillance of communicable diseases of national importance. *New Eng. J. Med. 268:* 182–192, Jan. 24, 1963.

MALAMUD, N., ITABASHI, H. H., CASTOR, J., and MESSINGER, H. B. An etiologic and diagnostic study of cerebral palsy: A preliminary report. *J. Pediat. 65:* 270–293, Aug. 1964.

MR 67: *A first report to the President on the Nation's progress and remaining great needs in the campaign to combat mental retardation.* President's Committee on Mental Retardation, Washington, D.C., 1967.

PERLSTEIN, M. A., and HOOD, P. N. Etiology of postneonatally acquired cerebral palsy. *JAMA 188:* 850–854, June 8,1964.

POSKANZER, D. C., and SALAM, M. Z. Mental retardation related to infectious disease in patients at Walter E. Fernald State School. In: *The Prevention of Mental Retardation Through Control of Infectious Diseases,* NICHD, Government Printing Office, Washington, D.C., 1968, pp 23–34.

A Proposal for a Pilot Study on the Incidence and Nature of Accidental Head Injury. Jaakko K. Kihlberg, Cornell Aeronautical Laboratory, Inc. of Cornell University and Warren Winkelstein, Jr., Dept. of Preventive Medicine, State Univ. of New York at Buffalo, 1967.

Report of the Mission to Denmark and Sweden. *The President's Panel on Mental Retardation. No 48.* Government Printing Office, Washington, D.C., 1962.

SWINYARD, C. A., SWENSEN, J., and GREENSPAN, L. An institutional survey of 143 cases of acquired cerebral palsy. *Develop. Med. Child Neurol. 5:* 615–625, Dec. 1963.

ZOLLINGER, R. W., CREEDON, P. J., and SANGUILY, J., JR. Trauma in children in a general hospital. *Amer. J. Surg. 104:* 855–860, Dec. 1962.

SESSION III

Perinatal Studies

Session Chairman: RICHARD L. MASLAND, M.D.

OBSTETRIC HISTORY OF GROSSLY RETARDED CHILDREN IN THE BOSTON SAMPLE OF THE COLLABORATIVE STUDY

Stewart H. Clifford, M.D.
The Boston Hospital for Women, Lying-In Division
Harvard Medical School
Boston, Massachusetts
James E. Drorbaugh, M.D.
The Children's Medical Center
Harvard Medical School
Boston, Massachusetts

This paper is an attempt to deal with the problem of the relationship of physical trauma to mental retardation in the Boston sample of the Collaborative Study on the Etiology of Cerebral Palsy, Mental Retardation and Other Neurologic Disorders. It is based on a detailed review of, first, children identified as having I.Q.'s below 80 at age four and, second, of children with severe retardation and cerebral palsy identified by age seven. The results, however, are only preliminary screenings.

Between 1959 and 1966, the Boston Hospital for Women, Lying-in Division (BLI), discharged 11,498 infants alive from its nurseries to become members of the Collaborative Study. The Children's Medical Center took over the study of these infants at the time of their one-year examination and is following them through seven years of age.

At the time the infant is discharged from the nursery, one of the protocol forms requires the pediatrician to give his conclusion as to whether the infant's condition was the result of anoxia or trauma. This is based on his observations from the time the head appears over the perineum and includes resuscitation, Apgar scores, initial examination, etc.

Including the collaborating institutions, there were 14,076 cases altogether who were subjected to the 4-year psychological tests. Initial analysis of three I.Q. categories: 69 or less, 70 to 79, and 80 or over, is presented in Table 1.

TABLE 1.—*Relation of neonatal etiologic impressions to 4-year I.Q.s*
All races--all birth weights

(Vertical %) Score	All Cases	Etiologic Impressions			
		Anoxia	Trauma	Both	None
69 or less	4.27	6.67	8.25	0	4.20
70 - 79	7.64	8.63	9.28	....	7.61
80 or over	88.09	84.71	82.47	....	88.19
Total Tests	14,076	255	97	7	13,717
Horizontal Percent	100	1.8	0.7	0.05	97.45

At the 4-year study, 4.27 percent had I.Q's below 70. This corresponds closely with the generally accepted incidence in this country of severe mental retardation. Approximately 12 percent had I.Q.'s below 80. There was only a slight increase in the neonatal diagnosis of anoxia in this group. Of the 97 infants judged to have suffered perinatal trauma, 17.53 percent had I.Q's below 80. Very similar data is obtained in relation to scores on the Graham Block Sort Test (Table 2).

TABLE 2.—*Relation of neonatal etiologic impressions to 4-year Graham Block Sort Test—All races—All birth weights*

(Vertical %) Score	All Cases	Etiologic Impressions Anoxia	 Trauma	 Both	 None
11 or Less	5.19	6.67	7.14	....	5.14%
12 - 20	5.71	8.89	7.14	....	5.65
21 or over	89.10	84.44	85.71	....	89.20
Total Tests	11,062	180	70	4	10,808
Horizontal %	100	1.62	0.63	0.04	97.70

TABLE 3.—*Collaborative Study—Incidence of various 4-year I.Q.s per 1000 exams—All races-all birth weights*

I.Q.	Total	Etiologic Impressions Anoxia	 Trauma	 Both	 None
69 or less	42.7	1.2	0.6	0	40.9
70 - 79	76.4	1.6	0.6	0.07	74.2
80 or over	880.9	15.3	5.7	0.4	859.4
All	1000.0	18.1	6.9	0.5	974.5

Despite the fact that 97.45 percent of all births were not considered to be complicated by either anoxia or trauma, the data in Table 3 does show an increased incidence of these events in the severely retarded. The incidence of neonatal anoxia was 28.1/1,000 children of I.Q. below 70 as compared with 18.1/1,000 of the total. The incidence of trauma can be calculated at 14.01/1,000 for the retarded compared with 6.9/1,000 for the entire group of 14,076.

Subanalysis of those with 4-year I.Q's below 80 for birth weight and race reveals a gross difference in the white and Negro populations in which other factors must far outweigh the demonstrated effects of low birth weight, trauma and anoxia (Table 4). At all birth weights, an I.Q. below 80 at age four was found in 4.72 percent of whites and 17.98 percent of Negroes. The white retardate was more likely to be of low birth weight and to have had a neonatal diagnosis of anoxia. Yet of all 4-year olds of I.Q. below 80, only 3.24 percent of whites and 1.95 percent of blacks had a recorded history of anoxia or trauma; thus prognosis on the basis of the obstetrical record becomes very difficult.

The second portion of the study involved only the 11,498 children discharged from BLI, and focused on the 87 children identified by seven years of age as severely mentally retarded, usually with an associated cerebral palsy. Table 5 lists what was considered the primary etiology based on the pediatrician's neon-

TABLE 4.—*Relation of neonatal etiologic impressions to 4-year I.Q.s. 79 or less—by race*

(Vertical %)	All Cases		Etiologic Impressions							
			Anoxic		Trauma		Both		None	
	W	N	W	N	W	N	W	N	W	N
All Birth Weights	4.72	17.98	6.92	29.16	14.58	20.40	0	20.00	4.59	17.98
2500 or Less	8.25	19.03	12.50	25.00	....	....	....	....	8.22	18.86
2501 or Over	4.49	16.90	4.88	30.98	15.22	21.74	....	....	4.39	16.73
Total All I.Qs.	6441	7635	159	96	48	49	2	5	6232	7485
Horizontal %	100	100	2.47	1.26	0.75	0.64	0.02	0.05	96.76	98.05

atal impression plus a comprehensive review of the genetic, obstetric and pediatric history.

TABLE 5.—*Incidence of mental retardation and cerebral palsy in the Collaborative Study patients delivered at the Boston Hospital for Women - Lying-in Division by probable etiology and birth weight*

	Birth Weight 2501 Grams or More 10,765 Live Births 25 Deaths in Hospital 10,740 Live Discharges		Birth Weight 2500 Grams or Less 892 Live Births 134 Deaths in Hospital 758 Live Discharges	
	Number	Rate Per 1000 Live Discharges	Number	Rate Per 1000 Live Discharges
Mongolism	6	0.56	5	6.60
Congenital Malformations	16	1.49	0	0
Mental Retardation in Family or Past History	14	1.30	0	0
Trauma Alone	3	0.28	2	2.64
Trauma & Other Complications	5	0.47	3	3.96
Asphyxia Alone	3	0.28	8	10.55
Asphyxia & Other Complications	5	0.47	6	7.92
Rubella Syndrome	2	0.19	2	2.64
?	6	0.56	1	1.32
Total	60	5.59	27	35.62
		87–7.57/1000		

The incidence of severe retardation was 7.57/1,000 for the entire group, 5.59/1,000 for the full-term and 35.62/1,000 for the prematures. Trauma alone was considered responsible for 5 of 87 cases or 6 percent of all cases of severe retardation; trauma plus other complications in 8 of 87 or 9 percent. Trauma with other complications was incriminated in 3 of 27 retarded prematures or 11 percent as contrasted to 5 of 60 full-term or 3 percent. A history of trauma was associated with subsequent severe retardation at a rate of 3.96/1,000 live prematures and of only 0.47/1,000 live full-term births, providing little evidence for trauma alone as a significant etiologic factor in severe retardation.

We then examined in greater detail the 13 children whose retardation or severe neurologic deficit was attributed to trauma. Five of the 13 cases were clear-cut trauma, but significant associated complications such as anoxia, genetic abnormality or hyperbilirubinemia were recorded in eight patients and outlined in Table 6.

Complications of pregnancy had occurred in six, including one toxemia, one bleeding, and two premature births with rupture of the membranes long before delivery. Neonatal observation of a CNS abnormality was made in 10 of the 13.

TABLE 6.—*Associated complications—trauma group*

Case	M.A. >34 yrs. <15 yrs.	Prev. Preg.	Gest.	Labor	Del.	G.A. <37 wks.	B. Wt. <2501 Gs.	5' Apgar <7	Bilirubin >15 mg%	Neonatal
*Cal.	0	0	0	0	+	0	0	0	0	+
*Cav.	0	0	+	0	+	0	0	0	0	+
Cala.	0	0	0	+	0	0	0	0	0	0
Bar.	0	+	+	+	+	0	0	+	0	+
Cat.	0	+	+	+	+	0	0	+	0	+
Cli.	0	0	0	+	0	0	0	0	+	+
*Whi.	0	0	0	+	+	0	0	+	0	0
Pro.	0	0	0	+	+	0	0	+	0	0
Gar.	0	0	0	+	+	+	+	0	+	+
*Spe.	0	+	+	+	+	+	+	0	+	+
Wal.	0	+	+	+	+	+	+	0	0	+
Ril.	+	0	0	0	+	+	+	0	0	+
Mel.	0	+	+	+	+	0	+	+	0	+
Total	1	5	6	10	11	4	5	5	3	10

*Indicates children with more mild conditions

TABLE 7.—*Kinds of trauma identified*

Case	Description
Cal.	Small midpelvis, arrested right occiput posterior, difficult pull, pitocin
Cav.	Markedly contracted pelvis, difficult mid-forceps delivery, marked molding
Cala.	Small anthropoid pelvis, scheduled for caesarean section, admitted in tumultuous labor, first stage 1 hr. 34 mins., second stage 4 mins.
Bar.	Occiput transverse, difficult delivery
Cat.	Cephalopelvic disproportion, undiagnosed occiput posterior, difficult forceps delivery
Cli.	Severe occiput molding caput, low forceps, moderate traction, fetal distress
Whi	Left occiput transverse, forceps rotation, firm traction, fetal distress
Pro.	Difficult breech delivery, fetal distress
Gar.	Hard labor, bloody amniotic fluid, left occiput transverse, mid-forceps difficult delivery, forceps applied 3 times, firm traction, symetric application
Spe.	Right occiput posterior, elective mid-forceps delivery, 5 minutes traction on head, deep forceps impressions molding and overlapping sutures
Wal.	Two attempts at axis traction, birth weight 2 lbs. 12 oz.
Ril.	Second of twins, compound presentation, left occiput transverse
Mel.	Right occiput anterior, prominent coccyx held head back against firm traction.

The specific types of trauma recorded in these 13 children and the nature of their neurologic deficits are listed in tables 7 and 8.

Only one child in the entire group (Cal.) had no other abnormality of the factors we examined. The 20-year-old mother was in her first pregnancy. She had a contracted pelvis and was scheduled for delivery by caesarean section, but entered the hospital at 40 weeks with ruptured membranes and delivered after an extremely hard labor. The baby showed no recognizable abnormalities in the immediate newborn period. His Apgar scores were 7, 8 and 8 and birth weight was 6 lbs. 13 oz. At the age of two he could not sit or walk, and a subsequent diagnosis was made of spastic quadriplegia and severe mental retardation.

More typical, perhaps, of the complicated case is an infant (Spe) who appeared to be severely damaged in the immediate newborn period but whose neurologic signs have gradually regressed to mild pyramidal tract involvement although his I.Q. was 74 at four years and 69 at seven years.

The mother was 33, had bleeding during the pregnancy, premature rupture of the membranes at 33 weeks. The baby weighed 3 lbs. 8 oz., was jaundiced, had an ABO (blood group) incompatibility and received two exchange transfusions. The contributing role of trauma is difficult to assess in such cases and supports the overall observation that perinatal trauma alone is less significant than many other factors in the etiology of mental retardation.

TABLE 8.—*Follow-up status—trauma group*

CASE	AGE	I.Q.	CLINICAL IMPRESSIONS
Cal.	3 yrs	—	Delayed Speech Development
	4 yrs	82	? CNS Damage
	7 yrs	102	Strabismus; Hyperactive; Poor School Performance
Cav.	4 years	101	Evidence of CNS Damage, Minimal Residual
Cala.	19 mos	—	*Spastic Quadriplegia
Bar.	2 yrs 10 mos	34	*Spastic Quadriplegia; Myoclonic Seizures
Cat.	3 yrs 8 mos	—	*Spastic Diplegia; ? Mental Retardation
Cli.	7 yrs	—	*Encephalopathy, Cortical Blindness, Seizures
Whi.	4 yrs	80	Hyperactive, Distractable, Mild Hemiparesis CP Clinic
Pro.	8 yrs	31	*Severe Encephalopathy
Gar.	3 yrs 3 mos	—	*Spastic Quadraplegia; Gross Motor and Mental Retardation
Spe.	4 yrs	74	
	7 yrs	69	Mild Bilateral Pyramidal Tract Signs
Wal.	4 yrs	<50	*Spastic Quadriplegia
Ril	4 yrs	38	*Mild Right Hemiparesis
	6 yrs	—	Epileptic; Hyperactive
Mel.	3 yrs	—	*Speech Development Retarded
	5 yrs 5 mos	—	Severe Mental and Motor Retardation

*Indicates more severe conditions

OBSTETRIC TRAUMA IN NEWCASTLE-UPON-TYNE

James K. Russell, M.D., F.R.C.O.C.
Gerald A. Neligan, M.D.
David G. Millar, M.D.
University of Newcastle-upon-Tyne
Princess Mary Maternity Hospital
Newcastle-upon-Tyne, England

A community study of every pregnancy involving a mother in Newcastle-upon-Tyne, a city of 270,000 in Northeastern England, was begun in January 1960 (fig. 1). It has been possible to follow up the great majority of the children born during the first three years of the survey. The health visitor, school doctors and nurses, and teachers supply information concerning health, development, and environment, making it possible to relate events in pregnancy and labor to the child's subsequent outcome.

Trauma and Fetal and Neonatal Death

In the 3-year period from 1960 to 1962, there were 14,524 pregnancies resulting in the delivery of 14,693 infants. Of these, 296 were stillborn and 253 died within four weeks. Autopsies were carried out in 465 (84.7 percent) of these deaths. In each case a team of pathologists, obstetricians, and pediatricians agreed on the cause of death after careful examination. "Trauma" was defined as "hemorrhage into and/or damage to intracranial structures or tissues elsewhere occurring during labor or delivery due to mechanical injury." Thirty-two (6.9 percent) of the deaths were attributed directly to trauma, and a further 14 deaths were associated with trauma.

Trauma and Mental Development

We are well aware of the "clustering" of various adverse factors that may limit a child's mental development: poor socioeconomic status, contracted pelvis in the mother with increased risk of "difficult" birth, prematurity, infection, and poor intellectual environment. However, the relative importance of each of these factors can only be elucidated in a study involving a complete population.

At the age of five, a few months after entering primary school, the children carried out the Goodenough "Draw-a-Man" test and other simple tests designed to measure hand-to-eye coordination and hand domination. So far, the obstetric antecedents have been related only to IQ as judged by the Goodenough test. The test has not been fully validated for this age group, and our interpretations must remain tentative until confirmed by more sophisticated measurement.

We examined the relationship between the mortality of certain complications and their effect on IQ in our study population—Pasananick's hypothesis. Table 1 shows the mortality rate of single legitimate pregnancies delivered in various ways, and the mean IQ of the survivors. The only type of delivery associated with significant reduction in IQ is breech delivery, which carries a large mortality. Therefore we examined the effect of breech delivery upon the survivors.

TABLE 1.—*Perinatal mortality and IQ with different methods of delivery*

	% Incidence	Perinatal Mortality Rate	IQ of Survivors
Spontaneous Vertex	85.4	21.0	113.3
Breech	2.7	230.4	109.0
Forceps Delivery	6.8	27.3	114.2
Caesarean Section	3.7	59.0	112.9

Significance

(Comparison of breech delivery with all other deliveries)

Mean IQ Breech Delivery 109.0

Mean IQ Others 113.2

Difference is highly significant $P < 0.02$.

Breech delivery was not associated with an increased incidence of physical handicap or mental defect. One hundred and thirteen infants delivered by breech were tested for IQ at age five. Table 2 shows the mean IQ in breech delivery as compared with that of infants delivered in other ways in different weight groups. Significant IQ differences persist in all weight groups. While in the population as a whole, the mean IQ rose with increasing fetal weight, the IQ of breech-delivered babies was lower in large infants than in infants of normal weight.

TABLE 2.—*Mean IQ in various groups*

Birth Weight	Breech Delivery			Other Deliveries		
	No.	%	Mean IQ	No.	%	Mean IQ
<5½ lbs	16	14.2	101.8	135	4.9	109.1
5½-8½ lbs	85	75.2	110.8	2203	79.6	113.1
>8½ lbs	12	10.6	105.9	429	15.5	114.9

Significance

In the comparison between individual weight groups the numbers are too small for the differences to be significant; however, when the groups are combined there is a significant difference in IQ which is independent of weight $(P - 0.05)$. The difference in mean IQ of various weight groups among infants not delivered by the breech is highly significant.

The mortality of breech delivery is lowest in the primigravida and highest in the grand multipara. IQ is highest in the offspring of the primigravida and lowest in the grand multipara. This again demonstrates the inverse relationship between IQ and perinatal mortality (Table 3). The IQ deficit associated with breech delivery persists in all of the major social-class groups (Table 4).

TABLE 3.—*Breech and vertex deliveries. Parity, perinatal mortality, and IQ of survivors (infants 5½ lbs.-8½ lbs. only)*

	Breech		Vertex	Breech Perinatal
	No.	IQ	IQ	Mortality Rate
Primigravida	27	113.7	112.9	177.3
Preg. 2,3,4.	40	111.8	114.4	243.2
Preg. 5 +	18	103.9	109.4	297.7

Significance

1. Difference in IQ between breech delivery and vertex delivery are not significant when the parity groups are combined together or separately.
2. The differences in IQ in different parity groups are significant at the 1% level in vertex deliveries.

TABLE 4.—*Social class and IQ — infants 5½-8½ lbs. only*

Social Class	Breech	Spontaneous Vertex
I and II	111.2	118.2
III	113.5	114.2
IV and V	102.4	109.0

Significance

The difference in IQ between breech and vertex deliveries is significant in Social Class III ($P<0.05$) but is not significant in other classes. The differences in mean IQ between social classes is highly significant ($P<0.01$) among vertex deliveries but not significant among breech deliveries.

Although breech delivery is associated with high incidence of short gestation and low birth weight, these differences do not wholly account for the IQ deficit. We believe that the actual trauma of delivery must be responsible to some extent.

Forceps delivery, another potentially traumatic method, presents a different picture. The IQs of children delivered by forceps do not differ significantly from those of children born by spontaneous vertex delivery, nor is there a significant difference between outlet and "difficult" forceps (Table 5). The slightly higher

TABLE 5.—*Forceps delivery, Newcastle 1960-61, primigravida only. Birth Weights 5½-8½ lbs.*

	No.	Mean I.Q.
Simple outlet Forceps	101	113.6
Mid Cavity Forceps	61	114.1
"Difficult" Forceps	11	109.2

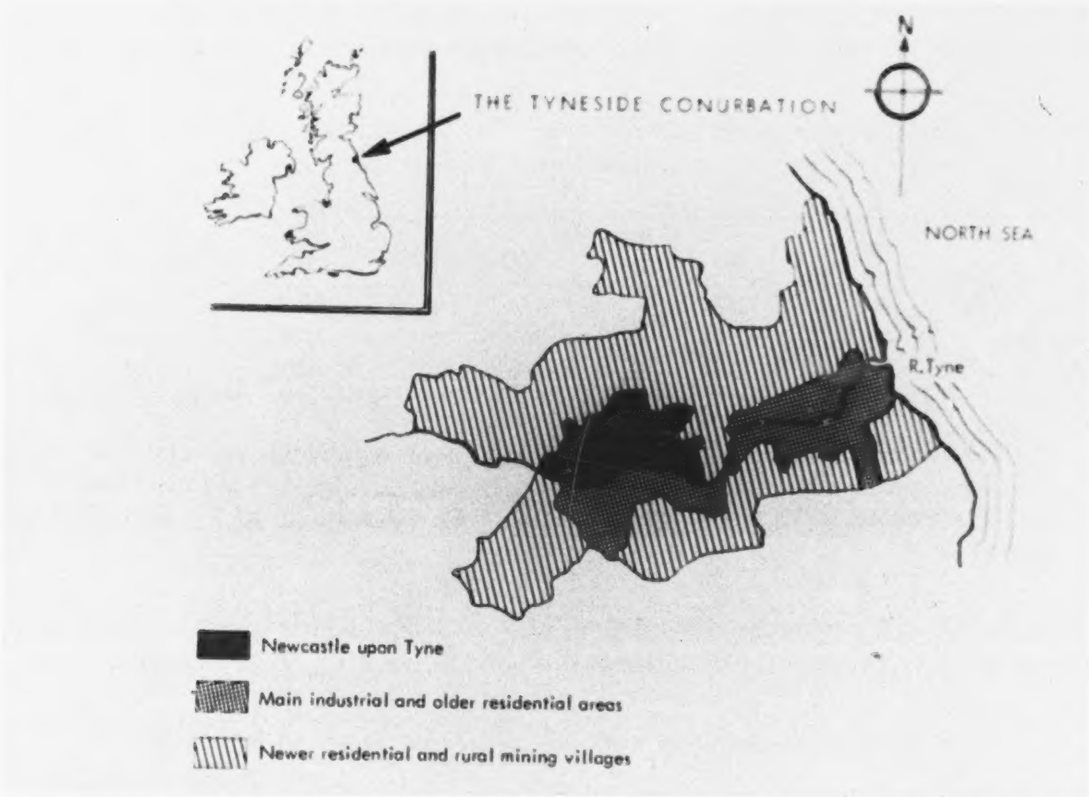

THE TYNESIDE CONURBATION
N
NORTH SEA
R.Tyne
Newcastle upon Tyne
Main industrial and older residential areas
Newer residential and rural mining villages

FIGURE 1.—The Tyneside conurbation, showing the area under study and socio-economic groupings.

IQ in the forceps deliveries is probably related to the high incidence of primigravidas and other social factors.

REFERENCES

FAIRWEATHER, D. V., et al: Perinatal mortality in Newcastle-upon-Tyne 1960-62. *Lancet* 1: 140–142, (Jan 15) 1966.

NELIGAN, G. A.: Paper read to Royal Society of Health, December, 1966.

RUSSELL, J. K., FAIRWEATHER, D. V., MILLAR, D. G., et al: Maternity in Newcastle-upon-Tyne; a community study. *Lancet* 1: 711–713 (Mar 30) 1963.

FETAL HEAD POSITION DURING DELIVERY, AND INTELLIGENCE

Lee Willerman, Ph.D.
Perinatal Research Branch,
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland

The mechanical forces of labor subject the infant's head to considerable compression, shearing, and molding. Holland (1922) and Schwartz (1956) report that these forces can injure the brain. Injury may be greater to one cerebral hemisphere than to the other. Churchill (1966) reported a greater incidence of ROA births (right occipito-anterior position of the fetus) among those patients who had epileptogenic foci situated in the left hemisphere; conversely, there were more LOA births (left position) among patients who had right-hemisphere foci. Similar observations were made in studies of asymmetric rhythmic activity in the EEGs (electroencephalograms) of newborns (Churchill, Grisell, and Darnley, 1966), in school-age children (Churchill and Rodin, 1968), and in patients with hemiplegic cerebral palsy associated with convulsive seizures (Churchill, 1966).

The present report includes two studies on intellectual differences in children born OL and OR. The premise is that the left hemisphere is endowed with greater capability for subserving verbal functions and that the right hemisphere has greater capacity for the development of performance functions (Penfield and Roberts, 1959). Left hemisphere injury at birth would then result in some loss of verbal intellectual potential, while right hemisphere injury would be followed by depression of performance potential.

Study 1

Ss were 212 children born at Henry Ford Hospital and enrolled prior to birth in a prospective study designed to relate obstetric events to neuropsychological deficits. *Ss* were 95 sibling pairs, both of whom had been delivered either from OL or OR vertex positions, and 22 children born from vertex positions, whose siblings had been born by breech or caesarean delivery. The mean ages of the OR and OL groups were almost identical. The age range at time of testing via the Wechsler Intelligence Scale for Children (WISC) was 5.0 to 9.5 years (mean = 7.5 years).

All *Ss* had birth weights exceeding 2.5 kg, with fetal lives free from complications. No illnesses associated with disturbed consciousness or neurologic abnormalities occurred after birth in this group. Only six *Ss* had been delivered by mid-forceps. No controls were provided for either the duration of labor or the use of drugs during delivery; it is assumed that these factors would be randomized between the OL and OR groups.

Results. Table 1 shows that mean Performance IQ is significantly higher than Verbal IQ among OR children. Among the OLs, mean Verbal and Performance IQs do not differ significantly.

TABLE 1.—*Mean WISC verbal and performance IQ as a function of position of head at birth*

Position at Birth	n	Verbal IQ	Performance IQ	D	^{s}D	t (paired)	p
OR	97	106.5	109.6	−3.10	1.10	2.82	.01
OL	115	106.3	105.2	+1.10	1.06	1.04	n.s.
Total	212	106.4	107.2	−0.80	0.77	1.04	n.s.

Results of a nonparametric analysis of these data in Table 2 indicate the frequency with which Performance IQ exceeded Verbal IQ in OR. Eight *S*s with equal Verbal and Performance IQs were excluded from this analysis.

TABLE 2.—*Superiority of either verbal or performance IQ as a function of position of head at birth*

	Position at Birth		
IQ	OR	OL	Total
Verbal>Performance	31	63	94
Verbal<Performance	60	50	110
	91	113	204 $X^2=9.54$, $p<.005$

ORs differed significantly from OLs in the relative frequency with which Verbal exceeded Performance IQ. Among the ORs, Performance IQ more frequently exceeded Verbal IQ ($X^2 = 8.80$, $p<.005$). For the OLs there was a nonsignificant trend for Verbal IQ to be higher ($X^2 = 1.50$, p=n.s.).

From the entire group of *S*s a subgroup was drawn of 58 sibling sets where one sib had been born OR and the other OL. The relative percentages for which the ORs performed better than their OL sibs were computed separately for same-sexed and opposite-sexed sets.

Among the same-sexed sets ($n=31$), the ORs differed significantly from the OLs. Only 28.6 percent of the OLs had higher Performance IQs than their same-sexed OR mates ($p<.05$, z score); whereas 63.3 percent of the OLs had higher Verbal IQs than their OR mates (n.s.). Among the opposite-sexed sets ($n = 27$), no significant differences as a function of position of birth were observed, although the trends were consistent with those shown for the same-sexed sets.

The results support the hypothesis that head position during birth is related to differences in verbal and performance functioning. When the occiput is situated in the right half of the maternal pelvis during delivery (OR positions), the majority of *S*s obtain lower Verbal than Performance IQs. Conversely, when the occiput is situated in the left half of the maternal pelvis (OL positions), there is a tendency for *S*s to have higher Verbal than Performance IQs.

Study 2

Ss were 213 children born in one of the Collaborative Perinatal Research Project's collaborating institutions.They were given the abbreviated version of the Stanford-Binet Intelligence Test, 3rd Rev. (Terman and Merrill, 1960) when four years old and an abbreviated WISC when seven years of age. The WISC included the following subtests: Information, Comprehension, Digit Span, Vocabulary, Picture Completion, Block Design, and Coding. There were 15 *Ss* included who had received the WISC at seven but not the Stanford-Binet at four.

The obstetric reports of head position during delivery were reviewed for each case coded as vertex delivery, and an effort was made to determine whether the child was in an LOA or ROA position during the birth process. Application of mid or low forceps during delivery was also recorded.

LOA and ROA infants did not differ significantly in birth weight, the means being 3,288.2 gm and 3,223.4 gm, respectively. The mean socioeconomic indexes (Myrianthopoulos and French, 1968) were virtually identical.

TABLE 3.—*Four-year Binet IQ as a function of head position during delivery and forceps*

	FORCEPS			
Head Position During Delivery	Mid	Low	None	Total
LOA	111.16 (n=23)	113.02 (n=50)	112.57 (n=47)	112.48 (n=120)
ROA	102.28 (n=18)	106.60 (n=30)	103.53 (n=30)	104.42 (n=78) *
Total	107.26 (n=41)	110.61 (n=80)	109.05 (n=77)	109.30 (n=198)

*t = 4.06, $p < .001$, df = 196 for Total LOA vs. Total ROA

Results. Table 3 presents 4-year Stanford-Binet IQs as a function of head position during delivery and the application of forceps. Over-all mean IQ for the LOAs is 8.06 points higher than that of the ROAs ($p < .001$). This difference remains significant when only the mid-forceps subgroups are compared, $t = 2.13$, $df = 39$, $p. < .05$; when low-forceps subgroups are compared, $t = 2.00$, $df = 78$, $p < .05$; and when no-forceps subgroups are compared, $t = 2.81$, $df = 75$, $p < .01$. Despite the trauma usually associated with mid-forceps, significantly lower IQ was not observed among those delivered in that fashion.

TABLE 4.—*Seven-year WISC verbal IQ as a function of head position during delivery and forceps*

	FORCEPS			
Head Position During Delivery	Mid	Low	None	Total
LOA	102.92 (n=25)	106.25 (n=48)	103.36 (n=50)	104.40 (n=123)
ROA	102.21 (n=19)	106.47 (n=30)	99.58 (n=28)	102.88 (n=77)
Total	102.71 (n=44)	106.33 (n=78)	102.00 (n=78)	103.81 (n=200)

Table 4 gives the mean 7-year WISC Verbal IQs. The over-all significant difference between ROAs and LOAs on the 4-year Binet is no longer observed at seven years of age on WISC Verbal IQ.

TABLE 5.—*Seven-year WISC performance IQ as a function of head position during delivery and forceps*

	FORCEPS			
Head Position During Delivery	Mid	Low	None	Total
LOA	105.48 (n=25)	107.60 (n=48)	107.83 (n=50)	107.26 (n=123)
ROA	108.00 (n=19)	103.63 (n=30)	105.40 (n=28)	105.35 (n=77)
Total	106.69 (n=44)	106.07 (n=70)	106.96 (n=78)	106.55 (n=200)

Table 5 presents the mean WISC Performance IQs. Here, no significant differences between LOAs and ROAs are observed. Further, there is no evidence that mid-forceps delivery is associated with either lower Performance or Verbal IQ. There may, however, be some unknown element of selection operating: e.g., only those mid-forceps cases not suffering from extensive trauma were able to take the 4-year and 7-year examinations.

The results suggest that there is differential impairment of intellectual potential associated with presumptive cerebral lesions occurring in neonates. As early as the time of birth, enough lateralized neuropsychologic differentiation appears to take place for injury to affect the individual's intellectual capacities. Those with presumptive neonatal left-hemispheric damage have depressed 4-year Stanford-Binet IQ.

REFERENCES

CHURCHILL, J. A. On the origin of focal motor epilepsy. *Neurology 16*: 49-58, Jan. 1966.

CHURCHILL, J. A., GRISELL, J., and DARNLEY, J. D. Rhythmic activity in the EEG of newborns. *Electroenceph. Clin. Neurophysiol. 21*: 131-139, Aug. 1966.

CHURCHILL, J. A., and RODIN, E. A. Asymmetry of alpha activity in children. *Develop. Med. Child. Neurol. 10*: 77-81, Feb. 1968.

HOLLAND, E. Cranial stress in the foetus during labour and effects of excessive stress on intracranial contents. *J. Obstet. Gynaec. Brit. Comm. 29*: 549-571, 1922.

MYRIANTHOPOULOS, N. C., and FRENCH, K. S. Application of the U.S. Bureau of the Census Socioeconomic Index to a large, diversified patient population. *Social Sci. Med. 2*: 283-299, Sept. 1968.

PENFIELD, W., and ROBERTS, L. *Speech and Brain Mechanisms*. Princeton Univ. Press, Princeton, N.J., 1959.

SCHWARTZ, P. Birth injuries of the newborn; morphology, pathogenesis, clinical pathology and prevention of birth injuries of the newborn. *Arch. Pediat. 73*: 429-450, Dec. 1956.

TERMAN, L. M., and MERRILL, M. A. *Stanford-Binet Intelligence Scale*. Manual for the Third Revision. Form L-M. Houghton Mifflin Co., Boston, 1960.

MATERNAL PELVIC SIZE AND NEUROPSYCHOLOGICAL OUTCOME

LEE WILLERMAN, PH.D.
Perinatal Research Branch
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland

This report explores the relationship of pelvic size to neuropsychological outcome, for difficulties during labor have often been assigned a major role in the presumptive etiology of mental retardation and cerebral dysfunction. Although the transverse measure of the pelvic outlet, the bi-ischial diameter, is only one of a number of important dimensions, it is treated alone in the present report.

Study 1

Ss selected for the first study were 212 seven-year-old children in the on-going Collaborative Perinatal Research Project sponsored by the National Institute of Neurological Diseases and Stroke, National Institutes of Health. All children are routinely administered a battery of psychological tests at ages four and seven. The present report deals only with the results of the 7-year psychological battery.

The *Ss* (14 *Ss* were Negro) included all children born in one of the collaborating institutions. They took an abbreviated WISC containing the following subtests: Information, Comprehension, Digit Span, Vocabulary Picture Completion, Block Design, and Coding.

The children were given the Tactile Finger Recognition Test (TFRT), adapted from the Halstead-Reitan-Indiana Neuropsychological Battery for Children. It requires that a blindfolded *S* identify which of his fingers is tapped in each of ten trials.

The maternal obstetric records were reviewed independently. Only those cases of vertex deliveries presenting in an occiput anterior position were considered further.

The range of the observed bi-ischial values was 7.0 cm to 12.5 cm in half-centimeter increments. The bi-ischial value nearest to the median included all those through 9.0 cm but less than 9.5 cm. This group was divided into a small-pelvis group (9.0 cm and smaller) and a large-pelvis group (9.5 cm and larger).

Though the children of large-pelvis mothers (LPMs) weighed slightly more than the offspring of small-pelvis mothers (SPMs), 3,311 gm to 3,201 gm respectively, this difference was not statistically significant; $t=1.42$, p=*ns*. The mean socioeconomic index was not significantly different for children of SPMs and LPMs; $t=0.82$, p=*ns*.

Results. Table 1 presents mean WISC Verbal IQs as a function of mothers' bi-ischial diameter and the application of forceps. A trend of only borderline significance ($p<.10$) suggests that children of SPMs have lower Verbal IQ. However, when just the *Ss* delivered without forceps are examined, a highly significant difference (8.54 points) emerges, indicating that offspring of LPMs have higher Verbal IQs ($t=3.89$, $df=86$, $p<.001$). Forceps delivery is not associated with significantly lower Verbal IQ.

TABLE 1.—*Mean WISC verbal IQ as a function of mothers' pelvic size and forceps delivery*

FORCEPS

Pelvic Size	Mid	Low	No	Total
Small	103.04 (n=20)	105.46 (n=46)	97.79 (n=33)	102.41 (n=99)
Large	102.25 (n=24)	107.11 (n=35)	106.33 (n=55)	105.71 (n=114)
Total	102.61 (n=44)	106.17 (n=81)	103.12 (n=88)	104.18 (n=213)

SUMMARY TABLE OF COMPARISONS

	t	*df*	*p* (two tailed)
All Small vs. All Large	1.80	211	.10
Small No vs. Large No	3.89	86	.001
Small Low vs. Large Low	.52	79	*ns*
Small Mid vs. Large Mid	.20	42	*ns*
Total Low vs. Total No	1.45	165	*ns*
Total Low vs. Total Mid	1.64	123	*ns*

Table 2 gives mean WISC Performance IQs as a function of pelvic size and forceps. Here, there is no statistically significant relationship between low Performance IQ and small pelvic size ($t=1.39$, p=*ns*). There was also no significant difference in Performance IQ between the forceps and no-forceps cases.

TABLE 2.—*Mean WISC performance IQ as a function of mothers' pelvic size and forceps delivery*

FORCEPS

Pelvic Size	Mid	Low	No	Total
Small	107.55 (n=20)	104.63 (n=46)	105.06 (n=33)	105.36 (n=99)
Large	105.75 (n=24)	107.74 (n=55)	108.44 (n=55)	107.66 (n=114)
Total	106.57 (n=44)	105.98 (n=81)	107.17 (n=88)	106.59 (n=213)

SUMMARY TABLE OF COMPARISONS

Comparison	*t*	*df*	*p* (two tailed)
Small vs. Large Pelvis	1.39	211	*ns*
Small No vs. Large No	1.27	86	*ns*

Table 3 gives the percent making at least one error on the TFRT as a function of pelvic size and forceps. While small pelvic size is not significantly related to percent error scores in the total sample, (*z* score=1.52, p=*ns*), the offspring OF SPMs delivered with forceps made significantly more errors than the offspring of LPMs (*z* score=2.29, $p< .05$).

TABLE 3.—*Percent tactile finger discrimination errors as a function of mothers' pelvic size and forceps*

FORCEPS *

Pelvic Size	Mid		Low		No		Total	
	% Error	n	% Error	n	% Error	n	% Error	Total n
Small	20.0	20	37.8	45	26.5	34	30.3	99
Large	13.0	23	18.2	33	26.3	57	21.2	113
Total	16.3	43	26.1	78	26.4	91	25.2	212**

*$X^2 = 2.30$, $p =$ ns for Total Small vs. Total Large

**$X^2 = 5.25$, $p < .05$ for All Small Forceps vs. All Large Forceps

Study 2

A second study utilizes the entire clinical evaluation of pelvic size—inlet, mid-pelvis, and outlet measurements—to determine whether such clinical judgments can contribute further to an understanding of the relationship of maternal pelvic size to psychological outcome. It includes gravidas having pelves judged as borderline or contracted and compares their offspring with children of gravidas having pelves estimated as adequate. Fetal head size and forces of labor are not considered in the present report.

Ss are 3,859 children born in one of the collaborating institutions. As part of the routine prenatal obstetric examination, the physician estimated whether the gravida's pelvic inlet, mid region, or outlet was "adequate," "borderline," or "contracted."

Vertex-born children whose 4-year IQs were available, and whose mothers had one or more pelvic regions coded as borderline or contracted (n=287), are designated the Inadequate group. One third of the small-pelvis sample were coded as having contracted pelves; the remainder were coded as borderline. Preliminary analyses revealed no differences between the contracted and borderline groups, and they are combined in the following analyses.

The control population came from children born in that hospital whose IQs were available and whose mothers were coded as having adequate pelves (n= 3,572).

Socioeconomic index, race, and birth weight did not differ significantly between the two groups. Birth weight of the Inadequate group was 3,129 gm; the Control group birthweight was 3,115 gm. The incidence of low birth weights (<2,501 gm) among the Inadequate and Control groups also did not differ significantly, 7.3% vs 7.4 percent, respectively.

Results. The mean Stanford-Binet IQ of the Inadequate group is 105.9; the mean IQ of the Controls is 107.0. The difference is not statistically significant. The groups were then compared for the frequency of occurrence of low IQs. Table 4 compares the frequency of IQs—85 of those *Ss* coded as Inadequate pelves with that of the Controls. Those *Ss* coded as Inadequate are subdivided into region of pelvic inadequacy. Only those Inadequates with small pelvic outlets differ significantly from the Controls ($p < .001$). While those with an inadequate inlet or mid-pelvis have a higher percentage of low IQs, these differences are not statistically significant.

TABLE 4.—*Percent IQs≤85 as a function of clinical estimates of pelvic adequacy**

PELVIS

	Small Inlet	Small Mid	Small Outlet	Controls
N	95	122	177	3572
%	7.4	6.6	10.2	4.6

*An Inadequate *S* may be represented in more than one pelvic region.
a $X^2 = 11.24$, $p < .001$ for difference between Controls and Small Outlet groups.

Table 5 includes only *S*s coded as inadequate. The Inadequates were arbitrarily classified into three categories: IQ≤85; IQ 86–119; and IQ≥120. The groups were contrasted for differences in the frequency with which the inadequate coding was assigned for each pelvic dimension.

TABLE 5.—*Type of maternal pelvic inadequacy as a function of IQ level* (*n*=*287*) *

PELVIC INADEQUACY LOCUS

IQ	n	Inlet		Mid		Outlet	
		f	%	f	%	f	%
85	21	7	33	8	38	18 [a]	85
86–119	217	72	33	89	41	135 [b]	62
120	49	16	32	25	51	24 [c]	47
Total	287	95	33%	122	43%	177	62%

SUMMARY OF COMPARISONS
X^2a-b = 4.61, $p < .05$
X^2a-c = 7.47, $p < .01$
X^2b-c = 3.15, $.10 < p > .05$

*Note: A mother may be represented in more than one pelvis category.

With respect to inadquate pelvic inlet, there are equal percentages of children in each IQ classification. For the inadequate mid-pelvis dimension, there is a slight but nonsignificant reversal: Differences between the highest IQ class and the two lower IQ classes are not statistically significant.

Only in the outlet measure do statistically significant differences emerge. Whereas 85 percent of the lowest IQ children have a coding of inadequate outlet, only 62 percent of the middle IQ group and 47 percent of the highest IQ class were so coded. The difference between the frequency of inadequate outlet in the middle and high IQ class is of borderline significance.

These results suggest that even among those judged inadequate, the locus of the judged inadequacy is related to lowered IQ.

NEUROPSYCHOLOGIC OUTCOME OF CHILDREN BORN VIA THE OCCIPUT POSTERIOR POSITION

ARTHUR L. ROSENBAUM, M.D.
Section on Pediatric Neurology
Perinatal Research Branch
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland

This study was designed to determine whether children born *via* the occiput posterior (OP) birth position have greater neuropsychological impairments than those born occiput anterior (OA). No evidence associating OP delivery with nervous system defects was found in the literature. One might suspect, however, that OP delivery carries a higher risk than OA, since in this position there is greater difficulty in obstetrical management, a higher incidence of pelvic contracture, and slightly prolonged labor in the mothers.

TABLE 1.—*Developmental measures in children born via the occiput anterior (OA) position compared with children born VIA occiput posterior (OP) position*

	Duration Pregnancy in weeks		Birthweight in kg		Bayley Scales				I.Q. Binet	
					Mental		Motor			
	OA	OP	OA	OP	OA	OP	OA	OP	OA	OP
N	220	221	220	221	218	216	218	216	220	221
X	40.0	40.1	3.421	3.388	82.6	81.5	33.7	33.1	109.7	104.4
t	0.185		0.741		2.404		1.225		3.922	
p	N.S.		N.S.		.05		N.S.		.001	

Cases selected for this study were 441 children born in one of the institutions participating in the Collaborative Perinatal Research Project sponsored by the National Institute of Neurological Diseases and Stroke. Detailed obstetrical records were obtained during pregnancy, and the offspring have been subjected to various neurologic and psychological examinations. At 8 months of age, each infant was evaluated by a psychologist who gave a standardized modification of the Bayley Scale of Infant Development. At one year of age a detailed neurologic exam was performed by a physician, and at 4 years of age the Stanford-Binet IQ test was administered by a psychologist.

The OP cases were culled from records indicating OP birth position just prior to delivery and a 4-year IQ score.

OP cases delivered by manual or mid-forceps rotation, or in the persistent OP position were chosen because of the obstetrical reliability of birth position determination within these groups in contrast to cases that rotated spontaneously to the OA position. The selected cases were compared with the OA population utilized by Willerman and Churchill in their study on fetal head position, reported elsewhere in this volume. Cases with a birth weight less than 2.5 kg were excluded. OP cases numbering 221 and OA cases numbering 220 were selected. Race, sex, and socioeconomic status did not differ significantly. OP cases were classified into LOP, ROP, and direct OP subgroups. Also recorded was whether mid-forceps rotation, manual rotation, or persistent posterior delivery occurred.

Outcome variables studied were: (1) duration of pregnancy in completed weeks of gestation; (2) birthweight; (3) Apgar scores at 1 min. and 5 min.; (4) Bayley mental and motor scores at 8 months; (5) Binet IQ at 4 years; (6) Plantar response at 1 year; (7) history of any kind of convulsive seizures during childhood; (8) a postural control rating scale. This scale, developed for the 1-year neurologic exam, is: 0 = walks free; 1 = cruises around furniture; 2 = must be led by hand; 3 = pulls self to standing; 4 = supports weight when held; 5= no support of weight or useful progression. A child was considered delayed when his score was 2 or more.

All data were subjected to student *t*-tests except the neurologic variables, which were analyzed by chi-square.

The OP offspring had significantly lower Bayley mental and Binet IQ scores. There were no significant differences in birthweight, duration of pregnancy, or Apgar scores.

TABLE 2.—*Mean Binet IQ scores as a function of fetal heaa position*

	LOA	ROA	ROP	LOP
N	128	92	118	74
X	112.9	105.2	104.8	103.4
pLOA	—	<.001	<.001	<.001
pROA	<.001	—	N.S.	N.S.

The LOA offspring had significantly higher Binet IQ scores than the ROA, ROP, or LOP offspring. No significant differences were found between the ROA group and the OP group or subgroups.

TABLE 3.—*Percent children displaying certain abnormal neurological characteristics as a function of fetal head position*

Characteristic	FETAL HEAD POSITION OP	OA	p
History of Seizures	8.6% (N=221)	4.5% (N=220)	N.S.
Delayed Postural Control (at 1 year)	9.3% (N=214)	18.3% (N=218)	<.01
Plantar Extensor Response (at 1 year)	7.1% (N=212)	20.7% (N=217)	<.001

Curiously, a significantly higher incidence of delayed postural control and plantar extensor responses at one year in the OA group was found. The OP group tended to have a greater incidence of seizures, but this was not statistically significant.

TABLE 4.—*Plantar extensor response at one-year neurologic exam as a function of fetal head position*

	Positive	Negative	Total N
LOA	25.4%	74.6%	126
ROA	15.3%	84.7%	91
			217*

*$p < .05$

Plantar extensor responses at one year of age were significantly higher in the LOA subgroup. No difference existed with respect to delayed postural control.

All OP cases in which a clear diagnosis of mid-forceps or manual rotation or persistent posterior delivery could be made were considered with respect to type of obstetrical management. Children born following manual rotation had significantly lower Bayley mental scores. No other significant differences were found.

TABLE 5.—*Development measures in children born via the occiput posterior position as a function of type of obstetrical management*

	Mid-forceps Rotation	Manual Rotation	Persistent OP Delivery
Duration of Pregnancy in weeks	40.1 (149)	40.1 (20)	39.8 (35)
Birth weight in kg	3.365 (149)	3.351 (21)	3.497 (35)
1 Minute Apgar Score	7.4 (149)	7.2 (21)	7.9 (35)
5 Minute Apgar Score	8.8 (140)	8.7 (18)	8.7 (34)
Bayley Mental Score	82.0 (144)	79.7 (21)*	81.8 (35)
Bayley Motor Score	33.5 (144)	32.2 (21)	32.8 (35)
Binet IQ Score	104.8 (149)	103.5 (21)	101.7 (35)

*$p = < .05$ when compared to mid-forceps rotation

In conclusion, 221 children born *via* the OP position were found to have lower Bayley mental scores at 8 months and lower Binet IQs at four years than 220 children born via the OA position. The mean Bayley mental score in the OP group was 81.5, compared with 82.6 in the OA. The mean Binet IQ of the former group was 104.4, compared with 109.7 for the latter. No significant differences were found with respect to race, sex, and socioeconomic status between the two groups.

However, children born via the OA position showed a significantly greater incidence of delayed postural control and plantar extensor response at one year of age then the OP group.

REFERENCES

BAINBRIDGE, M. N., NIXON, W. C., and SMYTH, C. N. Foetal weight, presentation, and the progress of labor. II. Breech and occipito-posterior presentation related to the baby's weight and the length of the first stage of labour. *J. Obstet. Gynaec, Brit. Comm. 68:* 748–754, Oct 1961.

BAYLEY, N. Mental growth during the first three years: A developmental study of 61 children by repeated tests. *Genet Psychol. Monogr. 14:* 1–92, 1933. (Modified in 1958 for use in the Collaborative Perinatal Project, Perinatal Research Branch, National Institute of Neurological Diseases and Stroke, Bethesda, Md.)

CALKINS, L. A. Occiput posterior—normal presentation. *Amer. J. Obstet. Gynec. 43:* 277–286, Feb. 1942.

CALKINS, L. A. Occiput posterior presentation. *Obstet. Gynec. 1:* 466–471, April, 1953.

CHEN, H. Y., and WEI, P. Y. Occiput posterior position. *J. Formosan Med. Ass. 61:* 1047–1060, Nov. 28, 1962.

D'ESOPO, D. A. The occipitoposterior position: Its mechanism and treatment. *Amer. J. Obstet. Gynec. 42:* 937–957, Dec. 1941.

MYRIANTHOPOULOS, N. C., and FRENCH, K. S. An application of the U.S. Bureau of the Census Socioeconomic Index to a large diversified patient population. *Social Science and Medicine. 2:* 283–299, 1968.

EFFECTS OF INTRAPARTUM UTERINE CONTRACTIONS ON THE EEG OF THE HUMAN FETUS

E. Garcia Austt, M.D., R. Ruggia, M.D., and Roberto Caldeyro-Barcia, M.D.
Servicio de Fisiologia Obstétrica
Facultad de Medicina
Universidad de la República
Hospital de Clinicas, piso 16
Montevideo, Uruguay

In advanced labor, uterine contractions may cause transient falls of fetal heart rate (FHR). Each fall (dip I) is simultaneous with the corresponding uterine contraction in such a way that the bottom of the dip I is synchronous with the peak of the contraction (Caldeyro-Barcia et al.).

There are many indications that uterine contractions causing dips I also cause a compression and deformation of the fetal head and probably a transient reduction of blood flow through the fetal brain. It is thus of interest to find out what changes occur in the fetal EEG during uterine contractions in advanced labor, and to correlate these EEG changes with the strength of the contraction and the variations occurring simultaneously in fetal heart rate.

Methods

The fetal EEG was recorded during advanced labor after rupture of the membranes, with cervical dilatation greater than 6–7 cm and the head at or beyond station 0. Several electrodes, made of silver and with hookshaped needles insulated except at the tip, were inserted in the occipital and parietal zones of the fetal head—the easiest to reach by the route employed (the birth canal). The electrodes were connected to a Grass electroencephalograph, whose paper speed is 1.5 cm/second.

The uterine contractions were inscribed by recording the intrauterine pressure with a thin polyethylene catheter introduced into the amniotic sac by transabdominal route or via the vagina and cervix. This catheter was connected to a pressure transducer and this to an 8-channel recording Poly Viso, with a paper speed of 1 cm/min (fig. 1). The pressure transducer was also connected to the Grass encephalographer by a Grass Balance Demodulator Unit; both the uterine contractions and the fetal EEG were recorded on the same paper (fig. 2).

The FHR was recorded by an instantaneous cardiotachometer triggered by the R wave of the fetal ECG. The ECG was obtained with a scalp electrode that

---

This study received support from the Pan-American Health Organization/World Health Organization, grant PR/URU/4101.

supplied a fetal signal free from maternal interference. The FHR tracing appeared both on the low-speed paper of the Poly Viso (fig. 1) and on the high-speed paper of the electroencephalograph (fig. 2).

In some patients, the maternal arterial pressure was also recorded in the Poly

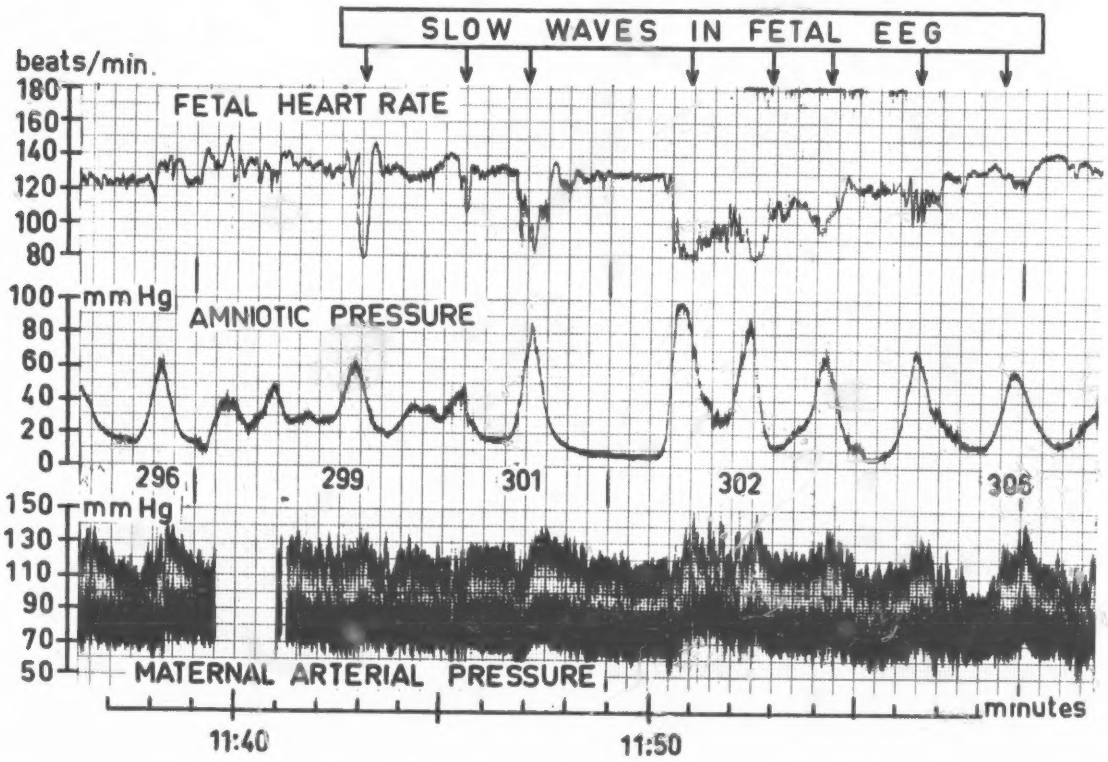


FIGURE 1.—Record #1969 (low speed) obtained during advanced labor in a normal pregnant woman at term. Full cervical dilatation. Fetal head in station +2 at hours 12:00. The effects on fetal EEG of contractions 301 and 306 are shown in figs. 3 and 4 respectively.

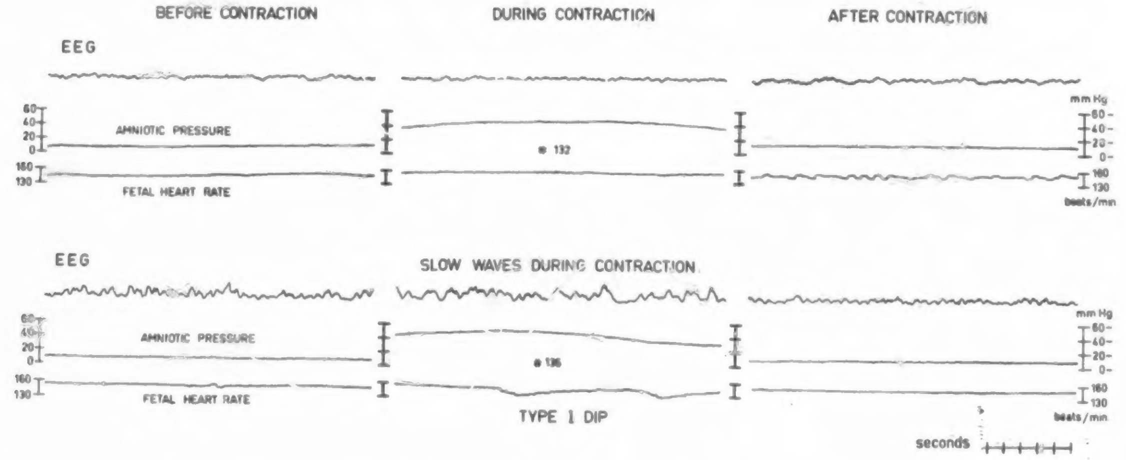


FIGURE 2.—Segments of records #2001 (high speed). Fetal EEG recorded with left-central occipital lead. During contraction 132 (peak amniotic pressure 50 mm Hg) no changes occur in fetal heart rate or EEG. During contraction 136 (peak pressure 60 mm Hg) slow waves appeared in the EEG and a type-I dip in FHR tracing (see also fig. 5).

Viso with a catheter introduced into the femoral artery and connected to a pressure transducer (fig. 1).

Results

The pattern of the fetal EEG changed during uterine contractions that were strong enough to cause rises of intrauterine pressure higher than 40–50 mm Hg. Usually these contractions also caused dips I in the FHR tracing.

The most frequently observed change in the EEG pattern was the appearance of high-voltage slow waves with a frequency of 0.5–2/sec and an amplitude of 50–70 uv. This change in the EEG pattern usually coincided with the peak of the contraction. It usually lasted 10–15 seconds.

Before and after the contraction, a faster low-voltage EEG pattern was recorded, with a frequency of 2–3/sec and amplitude of about 25 uv. The appearance of the slow-wave pattern was quite consistent in the subjects studied.

Figures 3 and 4 show intrapartum fetal EEGs illustrating typical examples of the change in pattern recorded during uterine contractions.

Figure 1 shows the corresponding tracing of uterine contractions and FHR obtained in the same subject but recorded at a lower speed. From contraction

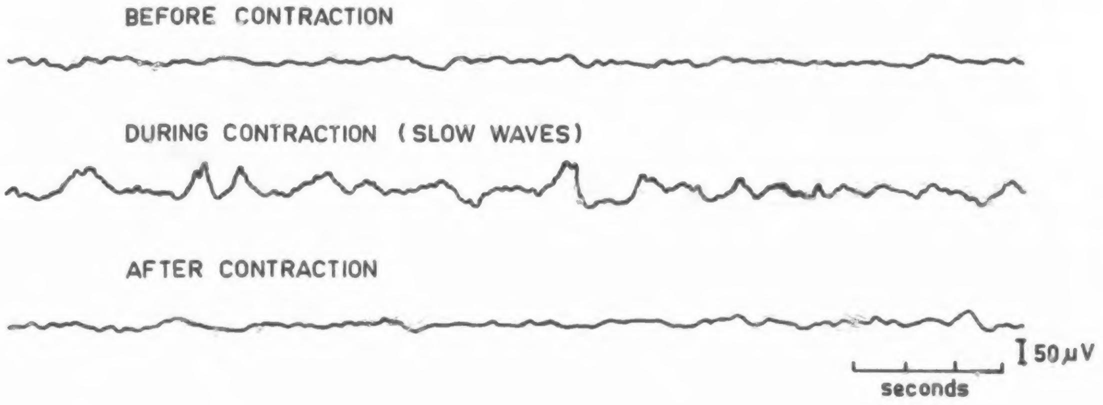


Figure 3.—Fetal EEG recorded during advanced labor. Record #1969 (high speed). Effects of contraction 301.

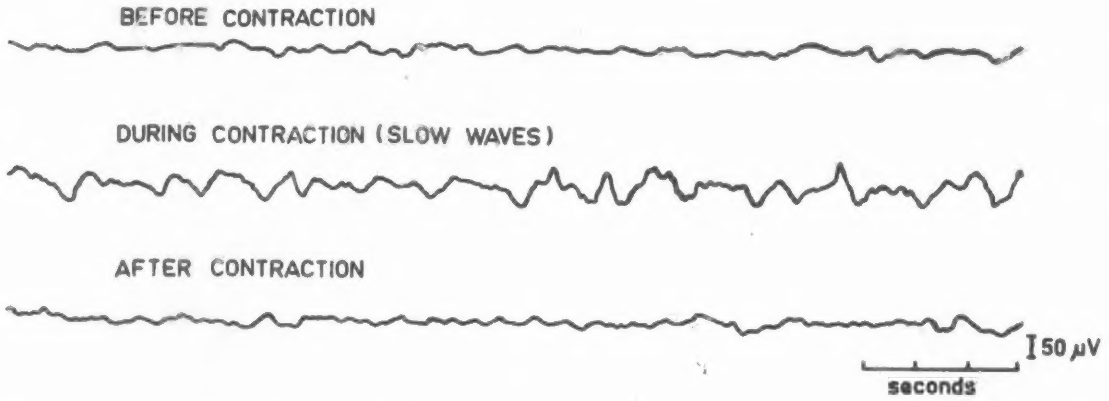


Figure 4.—Fetal EEG recorded during advanced labor. Record #1969 (high speed). Effects of uterine contraction 306 (see also fig. 3).

299 onward, each contraction caused a dip I in FHR and slow waves in the fetal EEG.

Figures 2 and 5 correspond to records obtained from another labor. Figure 5 is a segment of the low-speed record in which nine consecutive contractions are shown. The four strongest contractions (130, 133, 136, and 138), all having a peak pressure higher than 50 mm Hg, caused dips I in the FHR tracing. They also coincided with the appearance of slow waves in the fetal EEG, as illustrated for contraction 136 in fig. 2. The other five contractions shown in fig. 5 had a peak pressure lower than 50 mm Hg, did not cause dips I in FHR, and did not cause changes in the EEG pattern as illustrated for contraction 132 in fig. 2.

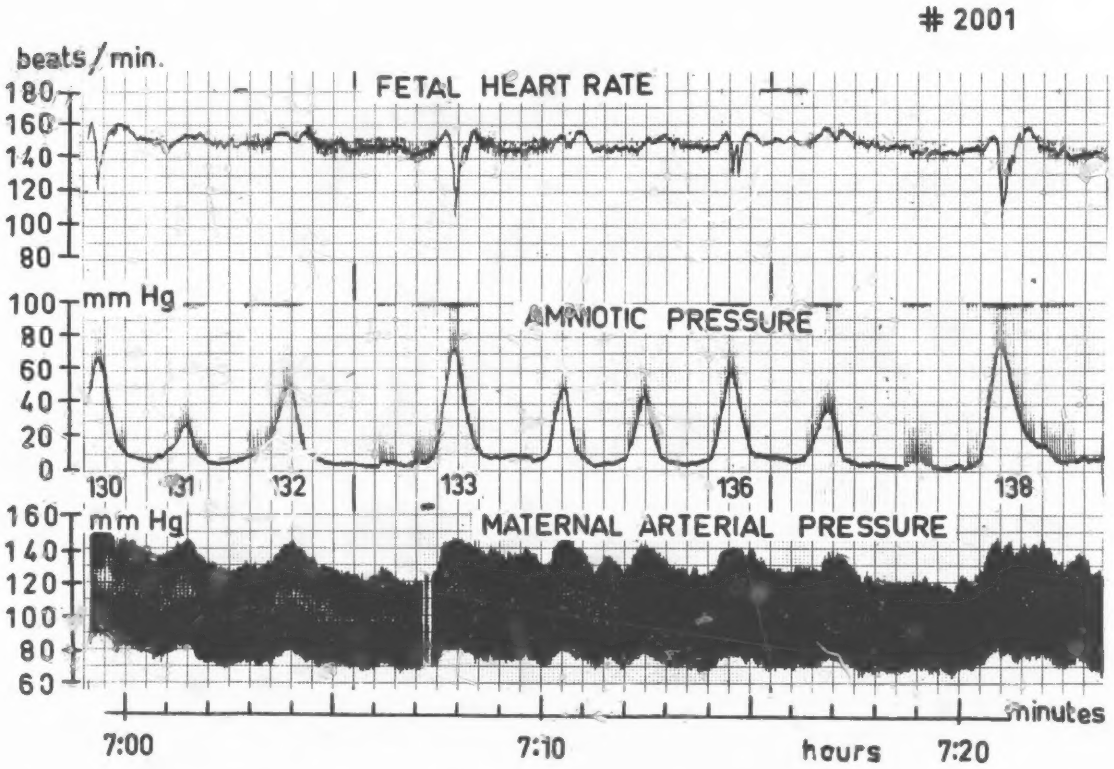


FIGURE 5.—Segment of record #2001 (low speed) obtained in advanced labor with ruptured membranes, full cervical dilatation, and fetal head in station +1. The effects of contractions 132 and 136 on the fetal EEG are shown in fig. 2.

Figures 6, 7, and 8 show a patient in whom the stronger uterine contractions caused slow waves in EEG without producing dips I in FHR. For example, contraction 105 had a peak pressure of only 30 mm Hg and caused no changes in FHR (fig. 8) or in fetal EEG (fig. 6). Contraction 106, which is stronger (peak pressure = 50 mm Hg), caused slow waves in fetal EEG (fig. 7) but no changes in FHR (fig. 8). Similar effects were observed for contractions 108, 109, 110, and 111, all with a peak pressure higher than 50 mm Hg. Contraction 114 caused slow waves in the EEG and a dip I in FHR.

At hour 7:09 (with a full cervical dilatation and the head in station +3), the left blade of the obstetrical forceps was inserted. A fall of great amplitude

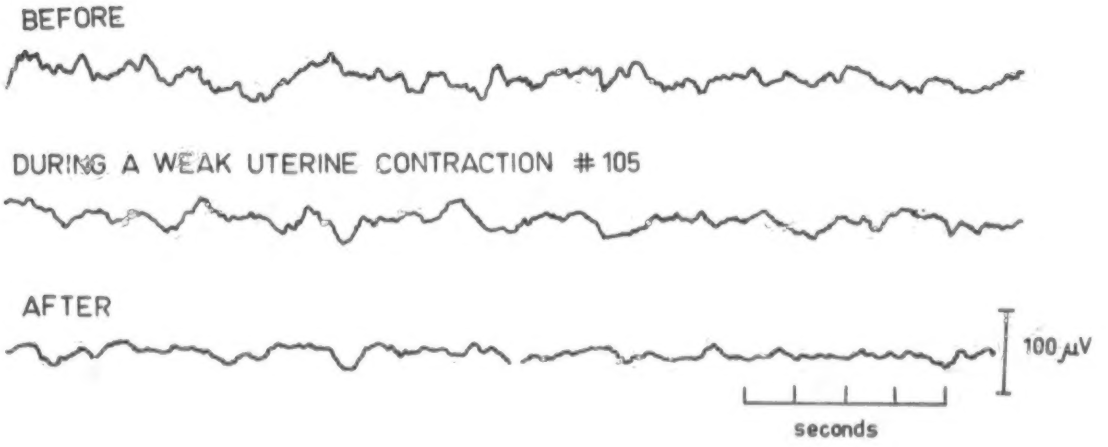


Figure 6.—Segment of record #2026 (high speed). The fetal EEG during labor obtained with the right contro-occipital lead shows no change before, during, or after a weak uterine contraction (105 in fig. 8) with a peak pressure of 20 mm Hg.

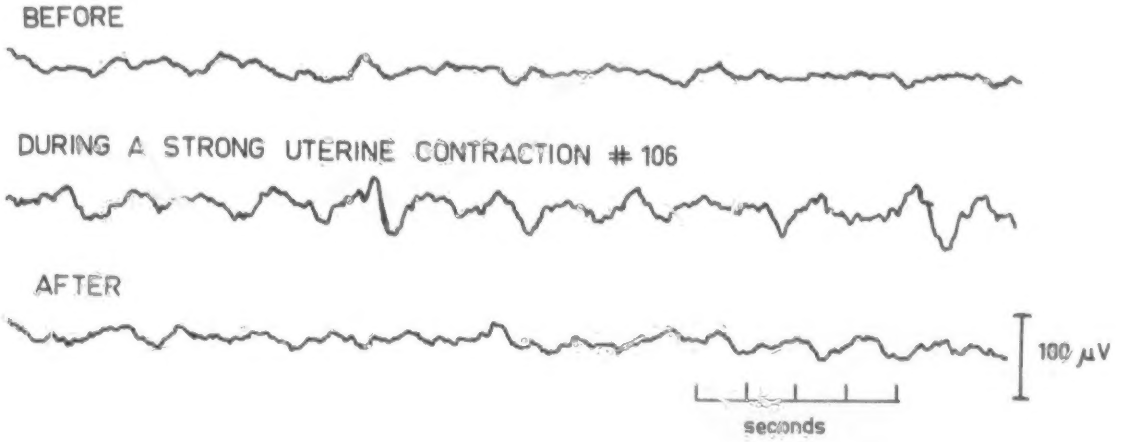


Figure 7—Continuation of record shown in fig. 6. Three minutes later. Slow waves appear in the fetal EEG during the peak of a strong uterine contraction (106 in fig. 8) with a peak pressure of 50 mm Hg.

and duration occured in the FHR tracing (fig. 8), and the fetal EEG (fig. 9) presented a low-voltage rhythmic discharge of 3–5/sec, which lasted approximately 30 seconds and was followed by a period of extinction.

Figure 10 corresponds to a different fetus and illustrates another rhythmic discharge in the EEG that started a few seconds after the peak of one uterine contraction. Before the onset of the contraction, the fetal EEG had a lower frequency and higher amplitude than usual. During the peak of the uterine contraction the prevalence of slow waves was greater than before the contraction.

During the descending limb of the contraction, a rhythmic discharge started and lasted approximately 40 seconds, with a progressive decrease in frequency. After the end of the discharge, slow waves were recorded for about 10 seconds. The initial EEG pattern was recovered after 35 more seconds.

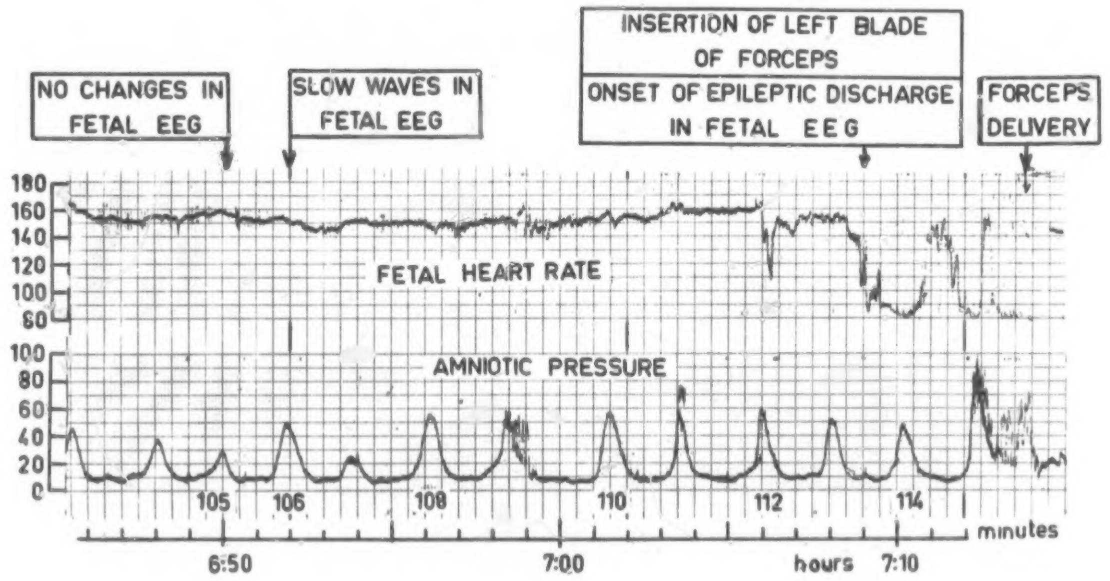


FIGURE 8.—Segment of record #2026 (low speed). Figures 6, 7, and 9 show segments of the EEG record at high speed.

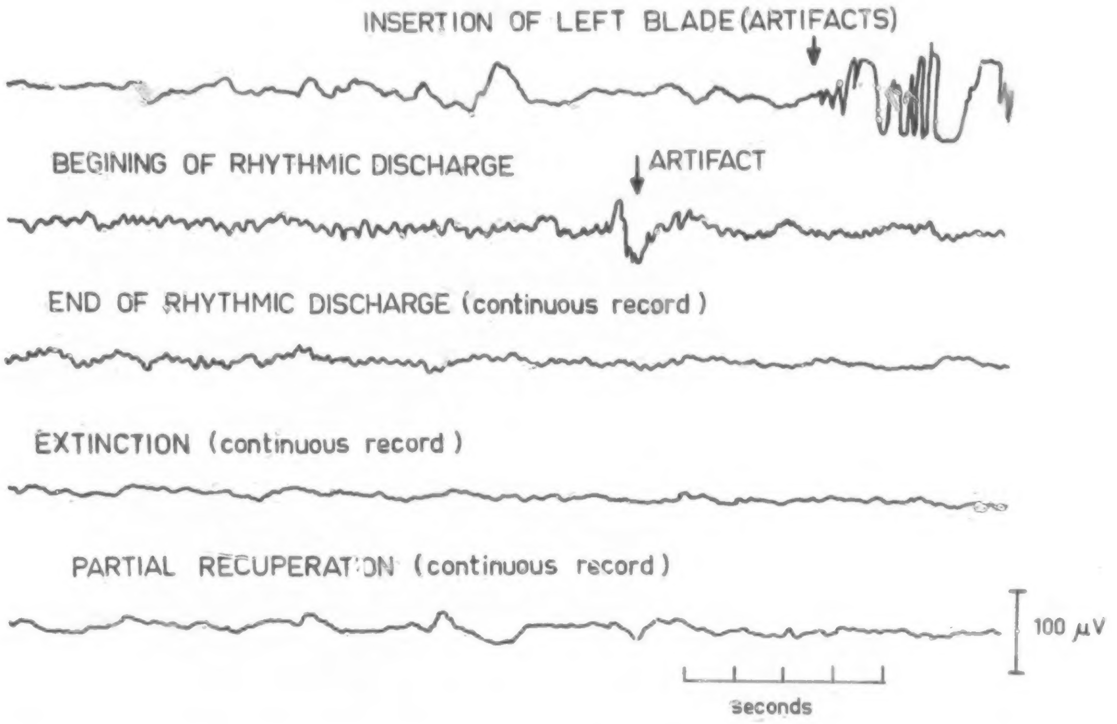


FIGURE 9.—Continuation of fetal EEG record (high speed). Shown in fig. 6 and 7. The initial part corresponds to hour 7:09 in fig. 8.

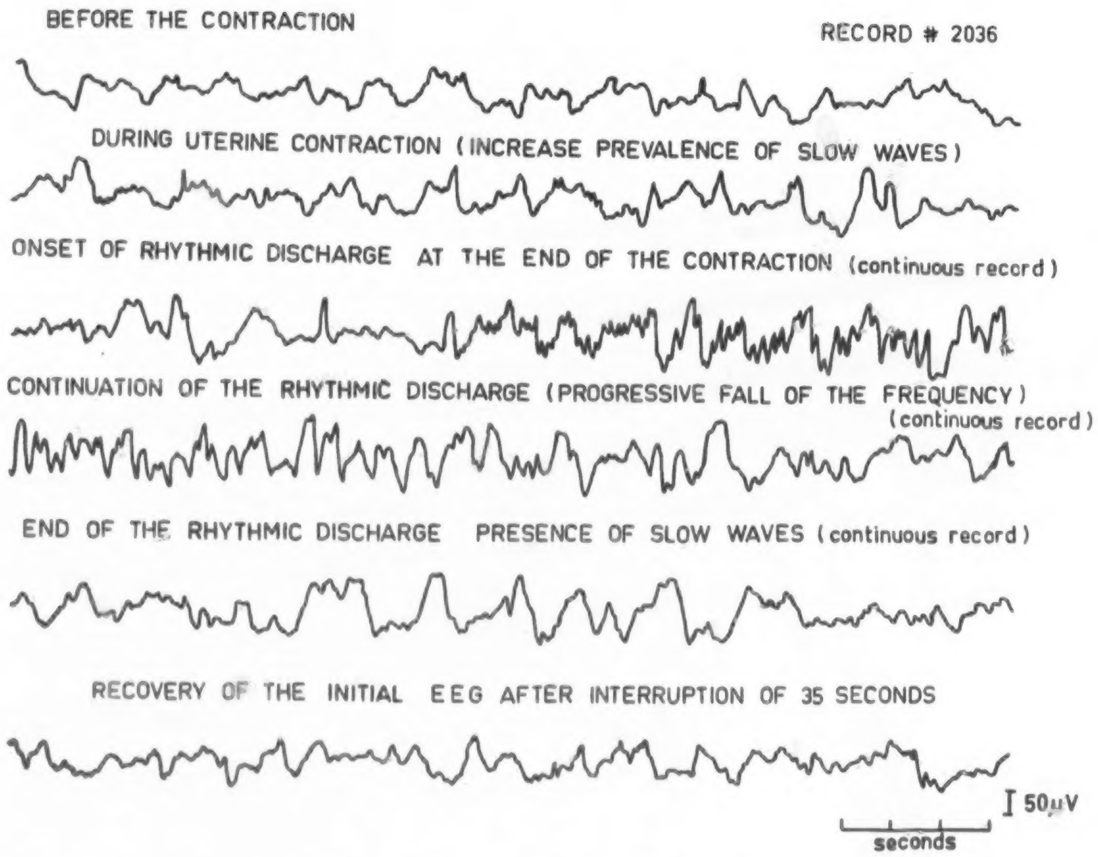


FIGURE 10.—Record #2036 (high speed). Rhythmic discharge starting after the peak of the contraction.

Discussion

The fetal EEG recorded between uterine contractions has the same characteristics as those described by Bernstine & Borkowski, Rosen & Satran, and Scoppetta, et al.

Rosen and Satran described the slowing down of the EEG rhythm during bearing-down efforts or when the fetal head is compressed by the obstetrical forceps. Changes in the EEG pattern similar to those seen during the peak of strong uterine contractions are known to occur in asphyxia or ischemia of the brain. Similar changes have also been reported by Mann in the fetal lamb when the ewe is made anoxic by breathing pure nitrogen.

The changes of the EEG of the human fetus reported in this paper occur under conditions in which it is very likely that the fetal head is being very strongly compressed by the uterine contractions. This transient compression may cause increased intracranial pressure, cephalic deformation, and consequent reduction in cerebral blood flow. Ischemia of the brain may explain the occurrence of slow waves and rhythmic discharges in the EEG during the peak of uterine contractions.

The association of slow waves in the EEG with dips I in FHR agrees with the hypothesis postulated above, since dips I are known to occur when the fetal head is strongly compressed by uterine contractions (Aramburu, et al.; Schwarcz, et al.).

Up to now there has been no evidence that these transient periods of brain ischemia cause permanent damage to the brain. As far as can be evaluated from the Apgar scores of the newborn, there is no correlation between the incidence of type-I dips during labor and the condition of the newborn.

In order to have more complete information on the long-term meaning of these intrapartum events, it will be necessary to follow the development of CNS functions in these children and correlate their performances with the changes that were observed in their fetal EEG and heart rates during labor. Such studies are currently under way.

REFERENCES

ARAMBURU, G., ALTHABE, O., and CALDEYRO-BARCIA, R.: Factors influencing intrapartum compression of fetal head and the incidence of dips I in FHR. *Physical Trauma as an Etiological Agent in Mental Retardation,* (ed.) by Carol Angle. Fourth Multidisciplinary Conference on the Etiology of Mental Retardation.

BERNSTINE, R. L.: *Fetal Electrocardiography and Electroencephalography.* Charles C Thomas, Springfield, Ill., 1961.

BERNSTINE, R. L., and BORKOWSKI, W. J.: Fetal electroencephalography. *J. Obstet. Gynaec. Brit. Emp. 63: 275–79, (Apr) 1956.*

BERNSTINE, R. L., and BORKOWSKI, W. J., Prenatal fetal electroencephalography. *Am. J. Obstet. Gynec. 77: 1116–19, (May) 1959.*

BERNSTINE, R. L., BORKOWSKI, W. J., and PRICE, A. H.: Prenatal fetal electroencephalography *Am J. Obstet. Gynec. 70: 623–30, (Aug) 1955.*

CALDEYRO-BARCIA, R., ET AL.: Control of human heart rate during labor. *The Heart and Circulation in the Newborn and Infant;* an international symposium presented by the Chicago Heart Association. ed. by Donald E. Cassels, 7-36. Grune & Stratton, New York, 1966.

LINDSLEY, D. B.: Heart and brain potentials of human fetuses in utero. *Amer J. Psychol 55: 412–16, 1942.*

MANN, L. I., PIRCHARD, J., and SYMMES, D.: EEG and EKG recordings during acute fetal hypoxia. Presented at the American College of Obstetricians and Gynecologists, Meeting of Districts II and IV, San Juan, Puerto Rico, October 9-12, 1968.

ROSEN, M. C., and SATRAN, R.: Fetal electroencephalography during birth. *Obstet. Gynec. 26: 740–45, (Nov) 1965.*

SCHWARCZ, R., ET AL.: Compression received by the head of the human fetus during labor. *Physical Trauma as an Etiological Agent in Mental Retardation,* (ed.) by Carol Angle. Fourth Multidisciplinary Conference on the Etiology of Mental Retardation.

SCOPPETTA, V., CURRO DOSSI, B., PAVONI, M.: L'ettroencefalografia fetale nelle gravidanze protratte. *Arch. Ostet. Ginec. 72: 320–24, (May–Jun) 1967.*

3

OBSTETRICAL FACTORS INFLUENCING INTRAPARTUM COMPRESSION OF THE FETAL HEAD AND THE INCIDENCE OF DIPS I IN FETAL HEART RATE

G. Aramburu, M.D., O. Althabe, M.D., and
Roberto Caldeyro-Barcia, M.D.
Servico de Fisiologia Obstétrica
Facultad de Medicina
Universidad de la República
Hospital de Clinicas, piso 16
Montevideo, Uruguay

A previous paper showed that when uterine contractions of labor exert a strong compression on the fetal head and this pressure is higher than the pressure in the amniotic fluid cavity, the fetal vagus is transiently stimulated and a transient fall (dip I) occurs in the FHR tracing.

Caldeyro-Barcia, et al, showed that dips I occur simultaneously with the contraction in such a way that the bottom of the dip is recorded almost at the same time as the peak of the contraction (fig. 1). Dips I have similar characteristics as the "early decelerations" described by Hon and Quilligan.

In this paper we shall discuss the influence of such obstetric factors as rupture of membranes on the incidence of dips I throughout labor and also the probable mechanism of action.

Twenty-six pregnant women at term were studied during labor. Intrauterine (amniotic) pressure and fetal heart rate were continously recorded throughout the entire labor. The progress of cervical dilatation and the station of the fetal head were periodically checked by vaginal examination.

Influence of the rupture of membranes. The production of dips I by uterine contractions was greatly facilitated by the rupture of membranes. Figure 1 shows a typical record illustrating such effect. Before the rupture of membranes, uterine contractions rarely caused dips I. After rupture of the membranes each uterine contraction caused a dip I of large amplitude.

Figure 2 and Tables 1 and 2 show the results obtained in 26 parturient women in whom FHR and amniotic pressure were recorded from the beginning to the end of labor. In 13 patients there was a loop of nuchal cord around the neck (Table 1); this complication was absent in the remaining 13 patients. The two groups of patients were analyzed separately.

This study received support from the Pan-American Health Organization/World Health Organization, grant PR/URU/4101, and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Public Health Service, Bethesda, Md., U.S.A.

In the 13 patients with nuchal cord, 1,076 uterine contractions were recorded before rupture of the membranes (Table 1). Only 52 (5 percent) of these contractions caused dips I. After rupture of the membranes, 725 contractions were recorded, and of these 295 (41 percent) caused dips I.

TABLE 1.—*Patients with nuchal cord*

	MEMBRANES		
	INTACT	RUPTURED	TOTALS
Total Number of Uterine contractions studied	1,076	725	1,801
Number of contractions that did not cause dips I	1,024	430	1,454
Number of contractions that caused dips I	52	295	347
Percentage of contractions that caused dips I	5%	41%	

The percentage of uterine contractions causing dips I was significantly higher after the membranes had been ruptured than before (chi 2 test, p 0.001).

A similar statement is valid for the group of 13 patients without nuchal cord (Table 2). In this group the percentages of contractions causing dips I were lower than in the first group.

TABLE 2.—*Patients without nuchal cord*

	MEMBRANES		
	INTACT	RUPTURED	TOTAL
Total number of uterine contractions studied	1,081	875	1,956
Number of contractions that did not cause dips I	1,058	652	1,710
Number of contractions that caused dips I	23	223	246
Percentage of contractions that caused dips I	2%	24%	

Interpretation of the effect of the rupture of membranes on the production of dips I. Our working hypothesis is schematically illustrated in fig. 3. When the membranes are intact there is some amniotic fluid around the fetal head. This fluid transmits the pressure equally in all directions, and the fetal head receives the same compression as the body of the fetus, umbilical cord, and placenta. Under these conditions uterine contractions caused no deformation of the head and no disturbances in cranial hemodynamics, and dips I are not produced.

After rupture of membranes there is no longer amniotic fluid surrounding

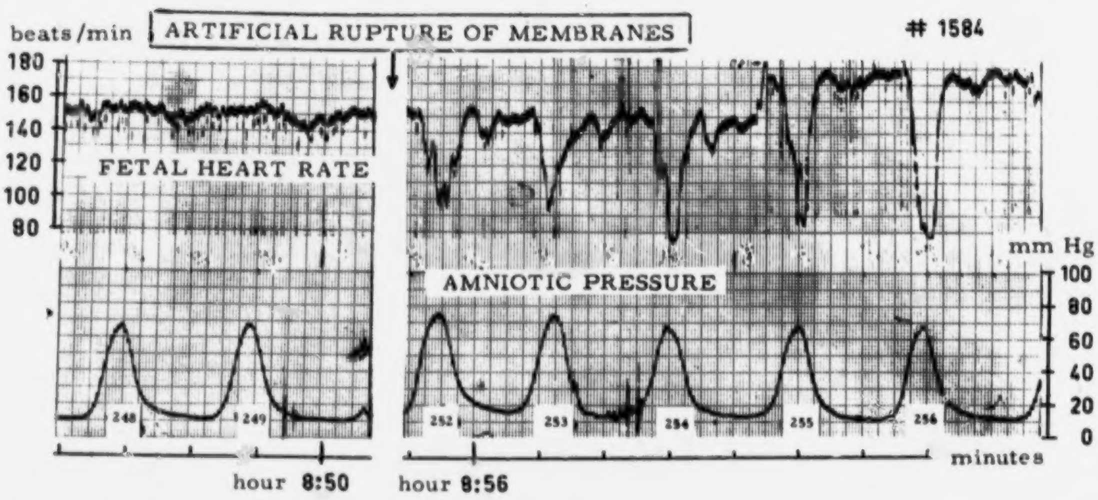
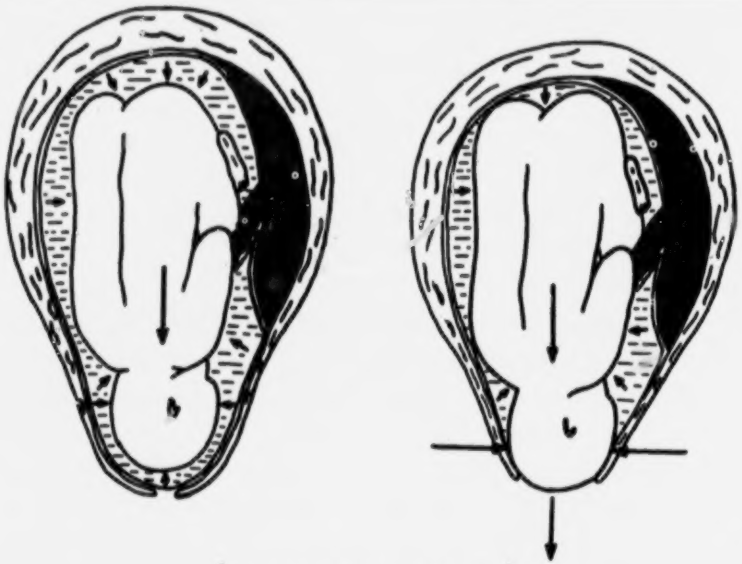


FIGURE 1.—Record obtained during the first stage of labor. Cervical dilatation 6 cm. Before the rupture of membranes, dips I are absent from the FHR tracin. After rupture of membranes each uterine contraction causes a dip I of large amplitude.

0 to 5 cm	CERVICAL DILATATION	5 to 10 cm
INTACT	MEMBRANES	RUPTURED
APPLICABLE	PASCAL LAW	NOT APPLICABLE
ABSENT	TYPE I DIPS	PRESENT



EQUAL	THAN ON THE REST OF THE FETUS	GREATER
PRESSURE EXERTED ON FETAL HEAD BY UTERINE CONTRACTIONS		

FIGURE 2.—Schematic illustration of the hypothesis postulated to explain the influences of the rupture of membranes on the incidence of dips I.

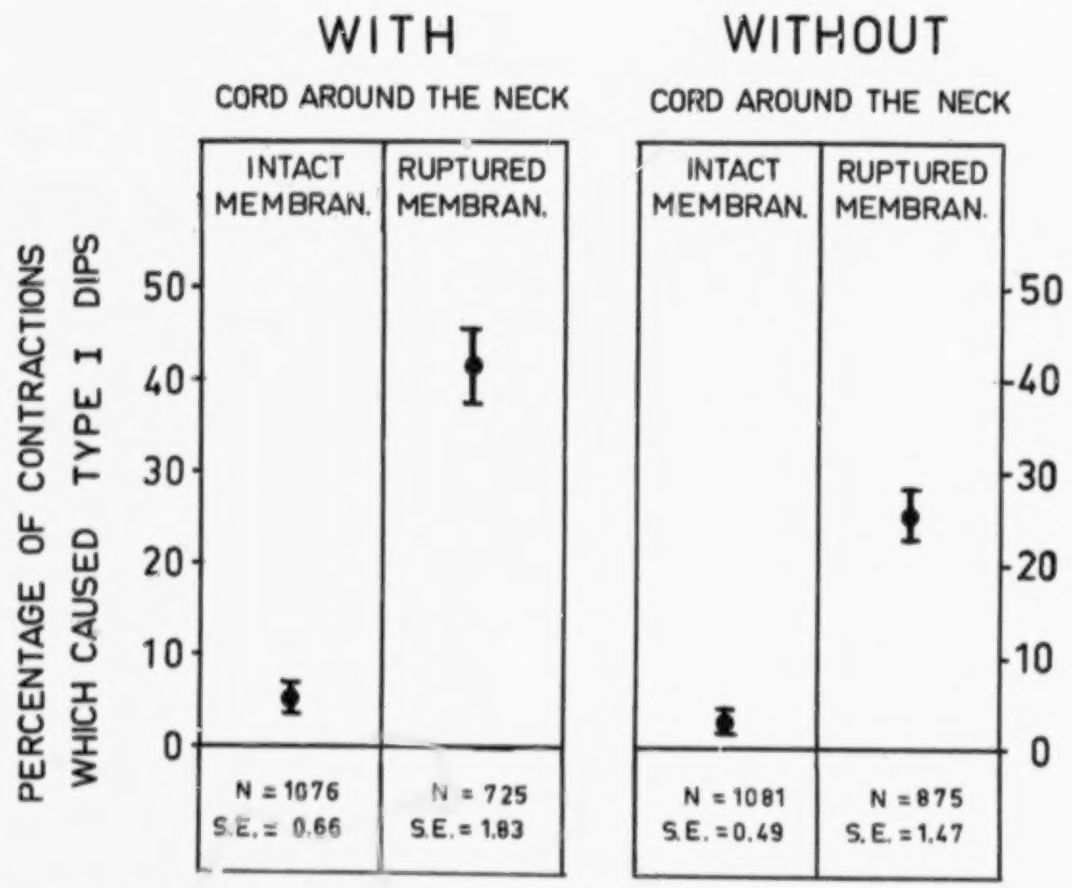


FIGURE 3.—The percentages of uterine contractions that caused dips I and the 95 percent confidence intervals are shown. The percentage is significantly higher after rupture of membranes than before. This statement holds true for fetuses with a loop of cord around the neck as well as those without such complication.

the fetal head. During each uterine contraction the pressure exerted at the equator of the fetal head is significantly greater than that in the amniotic cavity (Lindgren; Schwarcz, et al.).

The resulting marked rise of intracranial pressure will reduce blood flow through the brain, causing cerebral ischemia, hypoxia, and hyercapnia; all these disturbances are known to cause direct stimulation of the vagal center and thus explain the transient fall in FHR (dip I).

These disturbances also stimulate the vasomotor center and may cause fetal arterial hypertension, which in turn, acting through the baroreceptors of the carotid sinus and aortic arch, will reflexly stimulate the vagus, causing the fall in FHR (dip I).

Another possible mechanism of action is the following: When membranes are intact and amniotic fluid is present, the pressure exerted by uterine contractions is evenly distributed on all the nondeformed surface of the fetal head. After rupture of membranes the pressure on the equator of the fetal head is greatly increased, and there is no counterpressure at the vertex (which is exposed only to atmospheric pressure). During each contraction the fetal head can be greatly de-formed. This deformation may stimulate mechanically receptors in the face or head which could reflexly stimulate the vagus (Elsner, et al.).

The deformation of the cranial cavity may also disturb blood flow and contribute to cerebral ischemia eliciting the mechanisms previously described. Cerebral ischemia may explain the change in the EEG pattern (high-voltage slow waves) observed at the time of the peak of strong uterine contractions which produce dips I (Garcia Austt, et al.).

Effects of the progress of cervical dilatation on the incidence of dips I. The same 26 patients were divided into two groups of 13 each, according to the presence or absence of a nuchal cord.

The first stage of labor was divided in eight consecutive periods according to the values of cervical dilatation (fig. 4). The second stage became the 9th period

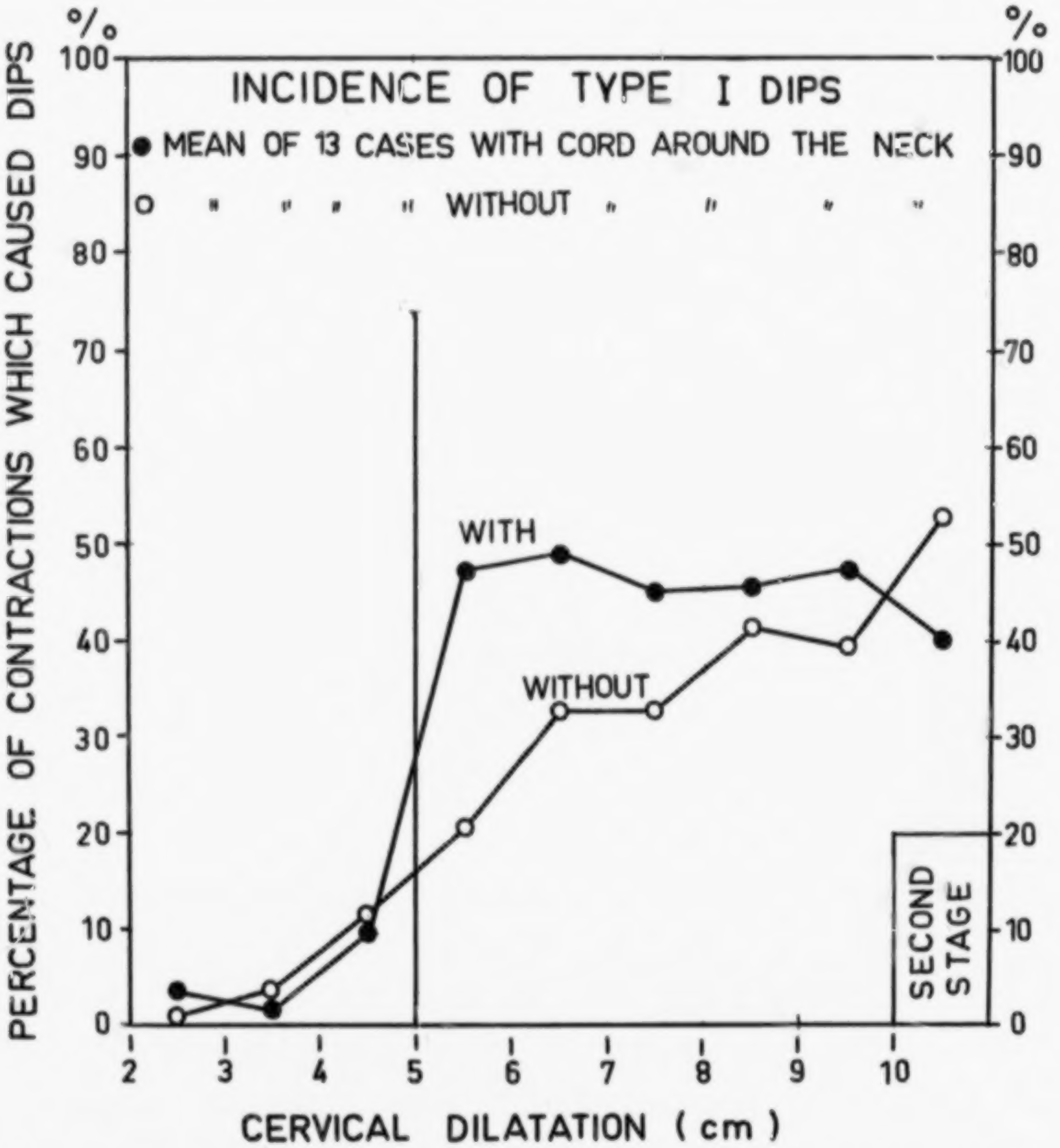


FIGURE 4.—The percentage of uterine contractions that causes dips I augments as cervical dilatation progresses.

studied (fig.4). A pool was made with all the contractions recorded during each of these nine periods in the 13 patients of a given group.

For example, in the group of 13 patients without nuchal cord, 221 contractions were recorded during the period when cervical dilatation was between 5 and 6 cm; only 45 of these contractions (20 percent) produced dips I (fig. 4).

The percentage of uterine contractions causing dips I increased as cervical dilatation progressed (fig. 4). This percentage was below 5 percent in early labor and about 45 percent in advanced labor. This difference is statistically significant. The previous statements were valid for both groups of patients. The increased percentage of contractions causing dips I might have been a direct consequence of the augmentation of cervical dilatation. It was very probably influenced, however, by the fact that in most of the subjects studied, the membranes were intact in early labor and ruptured in advanced labor (fig. 5).

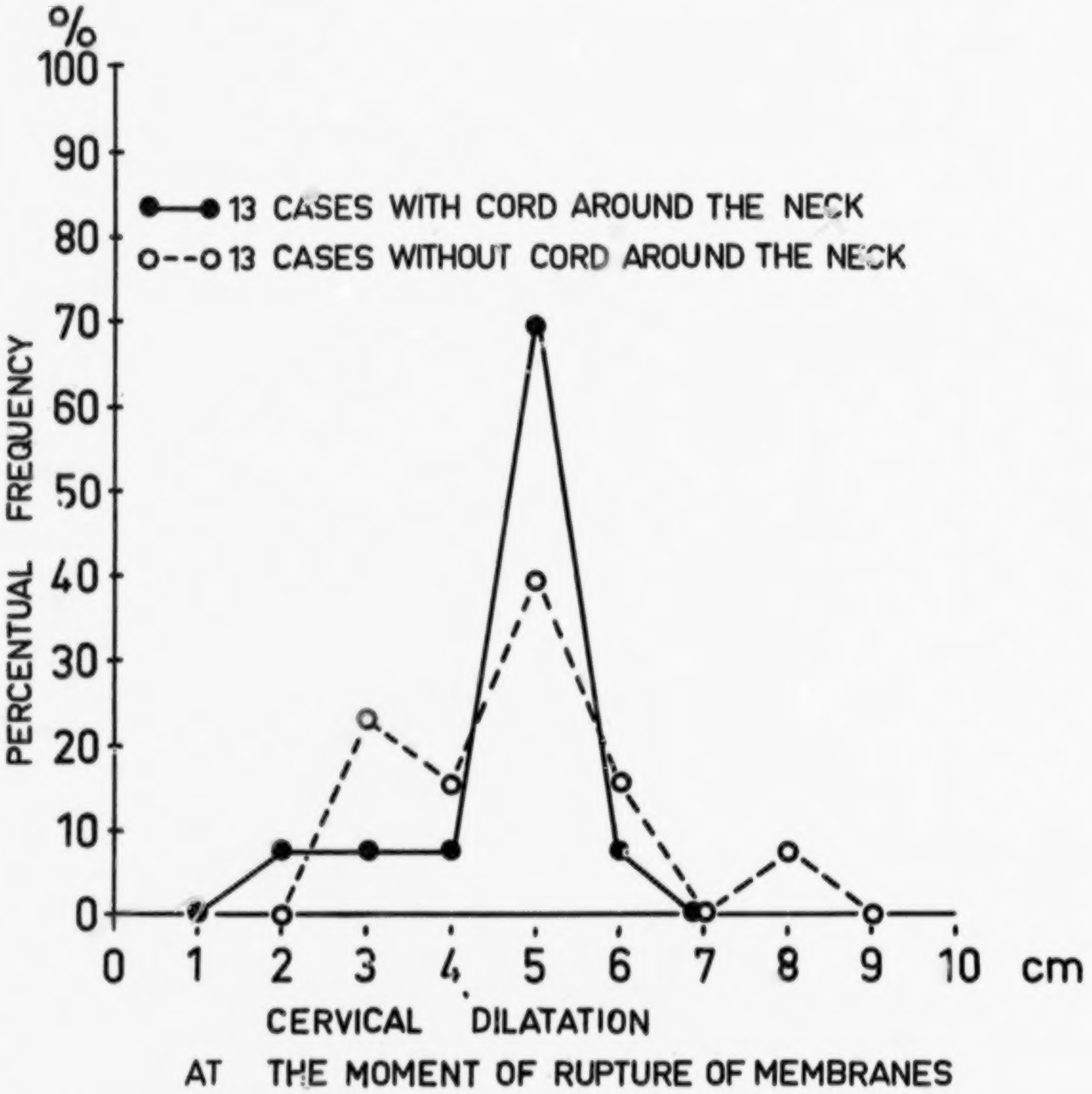


Figure 5.—Frequency polygons showing the percentage frequency corresponding to each interval of cervical dilatation at the moment of the rupture of membranes. Each polygon corresponds to one group of 13 parturient women; these two groups are the same as those in fig. 4.

Figure 5 shows that for the large majority of patients studied, the membranes were ruptured when cervical dilatation was between 3 and 7 cm.

Influence of the nuchal cord. In early labor and advanced labor (fig. 4) no significant differences were found in the percentage of contractions causing dips I between the two groups of patients. Only during mid-labor—when cervical dilatation was between 5 and 8 cm—was the percentage of contractions causing dips I significantly higher in the group with nuchal cord (fig. 4). This sudden rise may have resulted from the rupture of membranes performed at 5 cm of cervical dilatation in 9 of the 13 (70 percent) nuchal cord cases (fig. 5).

In the group of patients without nuchal cord, the incidence of dips I increased gradually as cervical dilatation augmented (fig. 4). This may have been related to the more even distribution of membrane rupture throughout the several periods of labor in this group of patients (fig. 5). Conversely, the lack of a sudden rise in the incidence of dips I at 5–6 cm of cervical dilatation in the patients without nuchal cord (fig. 4) may have resulted from the smaller percent-

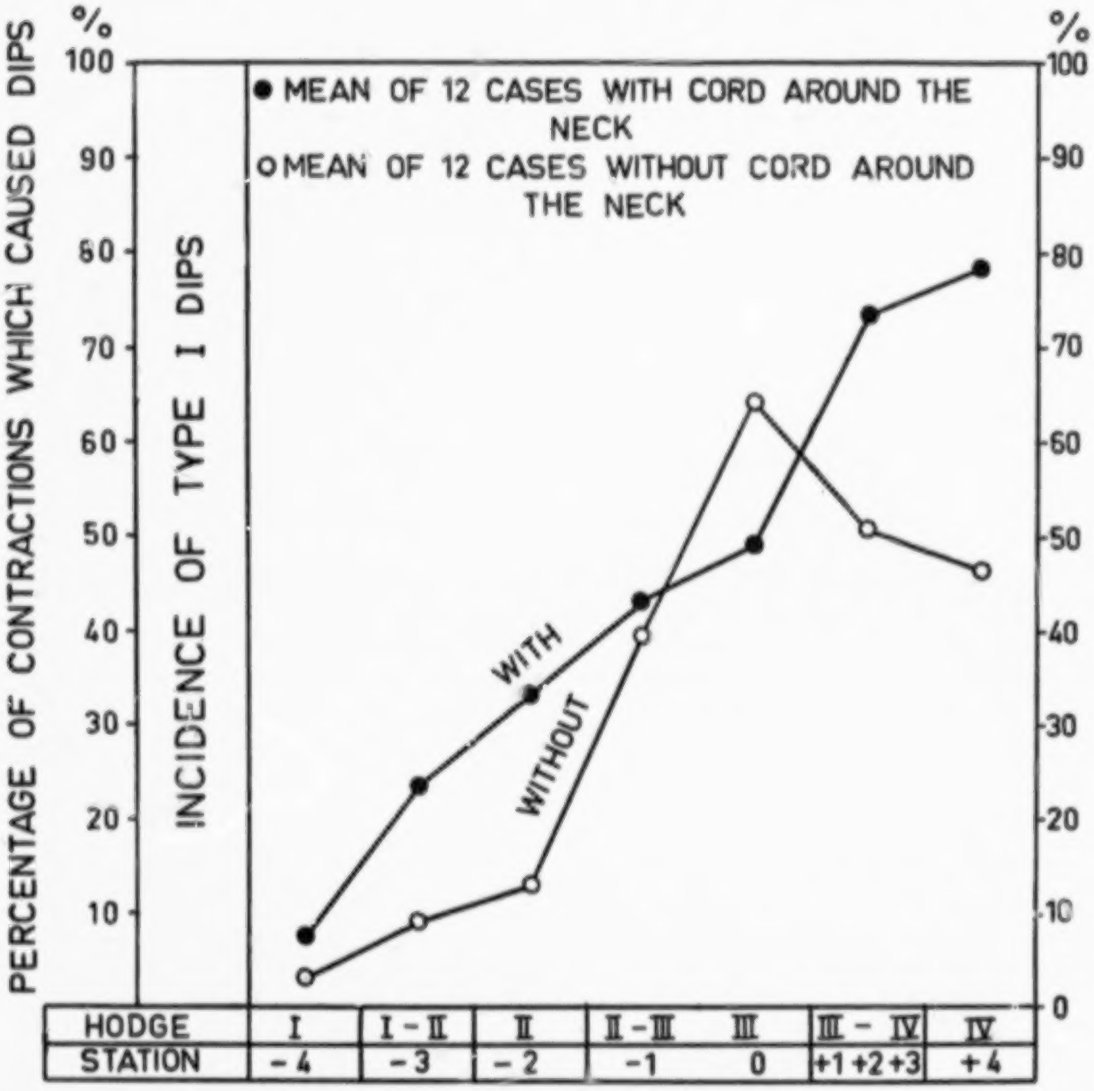


FIGURE 6.—The percentage of uterine contractions that causes dips I augments as the station of the fetal head progresses.

age (40 percent) of patients who had their membranes ruptured during that period of labor (fig. 5).

The results presented in this section agree with the hypothesis that the rupture of membranes is the main factor facilitating the production of dips I by uterine contractions. The role played in the pathogenesis of dips I by the progress in cervical dilatation *per se* and by the nuchal cord remains to be established.

Influence of the station of the fetal head on the incidence of dips I. Figure 6 shows that the incidence of dips I markedly augmented as the station of the fetal head progressed.

This augmentation was very regular for the subjects with nuchal cord. In the subjects without nuchal cord the incidence of dips I markedly augmented up until the fetal head reached station 0; thereafter, it exhibited a small fall.

The progress in the station of the fetal head may have facilitated its compression during uterine contractions, thus explaining the results here presented.

It should be noted, however, that progress of the station was associated with the increased percentage of subjects with ruptured membranes, a factor that may influence the results.

REFERENCES

CALDEYRO-BARCIA, R., et al. Control of human fetal heart rate during labor. In: *The Heart and Circulation in the Newborn and Infant.* An International Symposium presented by the Chicago Heart Association. D. E. Cassels (ed.), Grune & Stratton, New York, 1966, pp. 7-36.

ELSNER, R., et al. Cardiovascular defense against asphyxia. *Science 153:* 941-949, Aug. 26, 1966.

GARCIA AUSTT, E., RUGGIA, R., and CALDEYRO-BARCIA, R. Effects of intrapartum uterine contractions on the EEG of the human fetus. In: *Physical Trauma as an Etiological Agent in Mental Retardation.* C. Angle (ed.). Fourth Multidisciplinary Conference on the Etiology of Mental Retardation.

HON, E. H., and QUILLIGAN, E. J. The classification of fetal heart rate. II. A revised working classification. *Conn. Med. 31:* 779-884, Nov. 1967.

KELLEY, J. V. Compression of the fetal brain. *Amer. J. Obstet. Gynec. 85:* 687-694, Mar. 1963.

LINDGREN, L. The lower parts of the uterus during the first stage of labour in occipito-anterior vertex presentation; studies by means of intrauterine tokography. *Acta. Obstet. Gynec. Scand. 34:* 1-79 (Suppl. 2) 1955.

LINDGREN, L. The effect of rupture of the membranes upon the mechanism of labour. *Acta. Obstet. Gynec. Scand. 38:* 211-226, 1959.

SCHWARCZ, R. L., et al. Compression received by the head of the human fetus during labor. In: *Physical Trauma as an Etiological Agent in Mental Retardation.* C. Angle (ed.) Fourth Multidisciplinary Conference on the Etiology of Mental Retardation.

COMPRESSION RECEIVED BY THE HEAD OF THE HUMAN FETUS DURING LABOR

R. L. SCHWARCZ, M.D., G. STRADA-SÁENZ, M.D., O. ALTHABE, M.D.,
J. FERNÁNDEZ-FUNES, M.D., L. O. ALVAREZ, M.D., AND
ROBERTO CALDEYRO-BARCIA, M.D.
Servico de Fisiologia Obstétrica
Facultad de Medicina
Universidad de la República
Hospital de Clinicas, piso 16
Montevideo, Uruguay

Lindgren has reported that under certain conditions during labor the pressure exerted by uterine contractions on the fetal head may be 2 to 4 times higher than the pressure exerted on the amniotic cavity at the same time.

In 1927 Schwarcz and Salaber reported that the manual compression of the fetal head made through the anterior abdominal wall against the promontorium caused a sudden and marked fall of fetal heart rate (FHR) that was perceived by clinical auscultation. This finding has been confirmed by many authors and was recently studied with greater precision by means of the electronic record of FHR by Hon, Chung and Hon, and Arellano-Hernàndez, et al.

The falls of FHR caused by manual compression of the fetal head are mediated by the vagus nerve since they are completely blocked by atropinization of the fetus (Méndex-Bauer, et al.).

During advanced labor, particularly after rupture of the membranes, each uterine contraction may cause a transient fall of FHR (dip I), which is simultaneous with the contraction in such a way that the bottom of the dip I coincides with the peak of the contraction. It has been postulated that each dip I is caused by a strong compression caused in the fetal head by the corresponding uterine contraction (Caldeyro-Barcia, et al.). Cephalic compression would produce vagal stimulation.

Dips I have similar characteristics to the "early decelerations" described by Hon and Quilligan who have postulated the same pathogenetic mechanism.

The purpose of the present paper is to record and measure the compression received by the fetal head during each uterine contraction, correlating it with the rise in amniotic pressure and the amplitude of the dip I (if present).

This study received support from the Pan-American Health Organization/World Health Organization, grant PR/URU/4101, and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Public Health Service, Bethesda, Md., U.S.A.

Methods

This study was made in 18 normal-term pregnant women with vertex presentation. The pressure received by the fetal head during labor was recorded by three flat pressure receptors introduced between the uterine cervix and the fetal head (fig. 1) outside the ovular membranes.

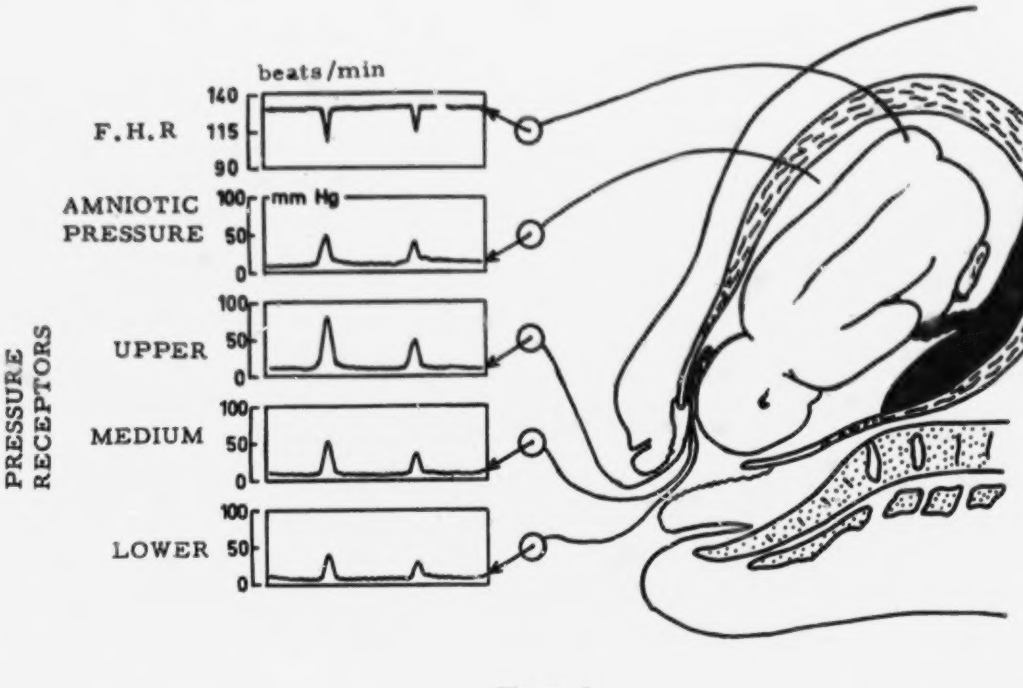


Figure 1

Each pressure receptor was a flat tambour (fig. 2) closed by two latex membranes glued to the edge of a circular hold made on a thin plastic blade. The diameter of each receptor was 15 mm. The distance between the centers of two consecutive receptors was 30 mm. Each receptor was filled with water (without bubbles) and connected to a recording pressure transducer by a thin polyethylene tube.

The three receptors were centered in line on the blade; they are known as "upper," "medium," and "lower," according to the position in relation to the uterus. The flexible plastic blade was 10 cm long, 3 cm wide, and 1 mm thick.

The blade was introduced between the membranes and the uterus toward the fundus. One surface of the receptor contacted the lower pole of the amniotic sac and eventually the fetal head; the other faced the uterine wall. The lower end of the blade was sewn to the uterine cervix at the external os (fig. 2).

The position of the receptors relative to the fetal head was determined by radiology. As labor progressed, and the cervix was "taken up," the attached blade and receptors moved from the vertex toward the base of the fetal cranium (fig. 3).

The intrauterine (amniotic) pressure was recorded by a catheter introduced through the abdominal and uterine walls into the amniotic sac. This catheter was connected to a pressure transducer (fig. 2).

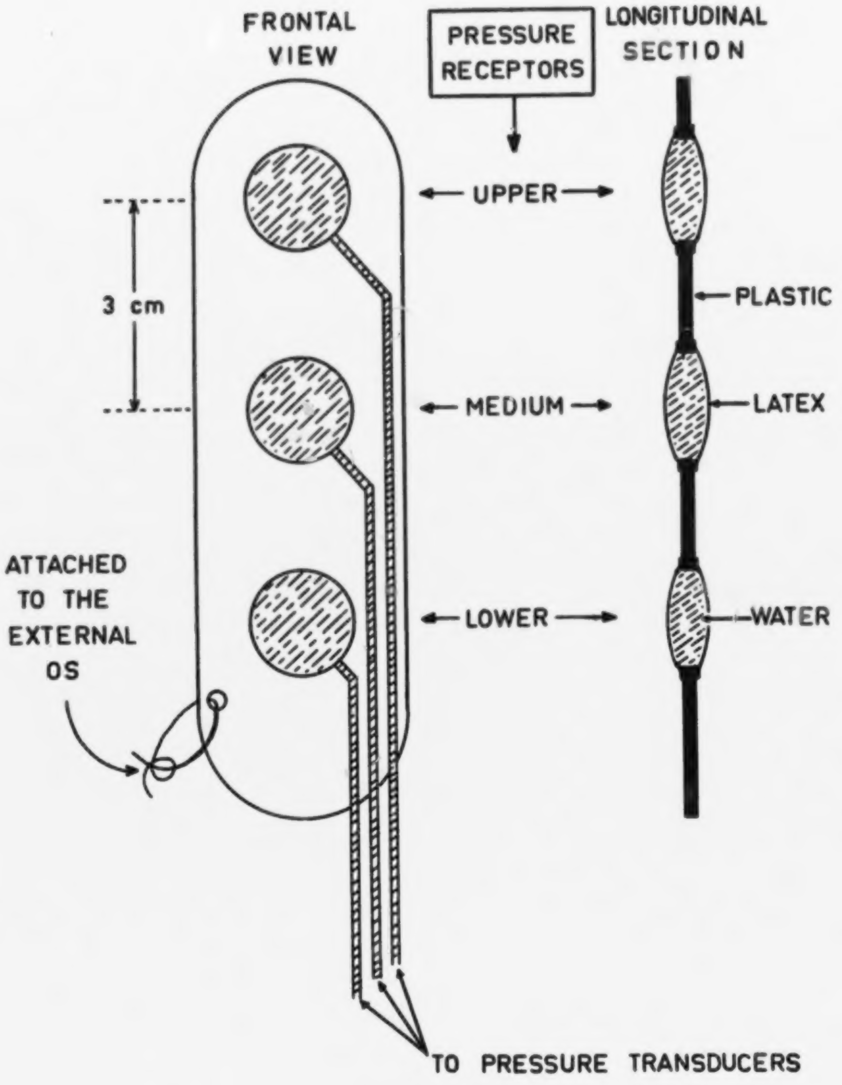

FRONTAL VIEW
PRESSURE RECEPTORS
LONGITUDINAL SECTION
UPPER
3 cm
PLASTIC
MEDIUM
LATEX
ATTACHED TO THE EXTERNAL OS
LOWER
WATER
TO PRESSURE TRANSDUCERS

Figure 2

The fetal heart rate was recorded by an instantaneous cardiotachometer triggered by the fetal ECG. The ECG was obtained, almost free from maternal interference, by electrodes inserted under the skin of the fetus, either in the buttock (fig. 1), the scalp, or both.

The amniotic pressure, FHR, and pressures between the fetal head and birth canal were all inscribed on the same recording paper (figs. 1, 4, and 5) to facilitate the study of their interrelations.

Results

During each uterine contraction, the pressure recorded by the cephalic receptors rose almost simultaneously with the amniotic pressure (figs. 4 and 5). The amplitude of the pressure rise was measured in every tracing for each contraction (fig. 5). The pressure rise in each cephalic receptor was plotted against the corresponding rise in the amniotic pressure (figs. 3 and 6). For any given period of

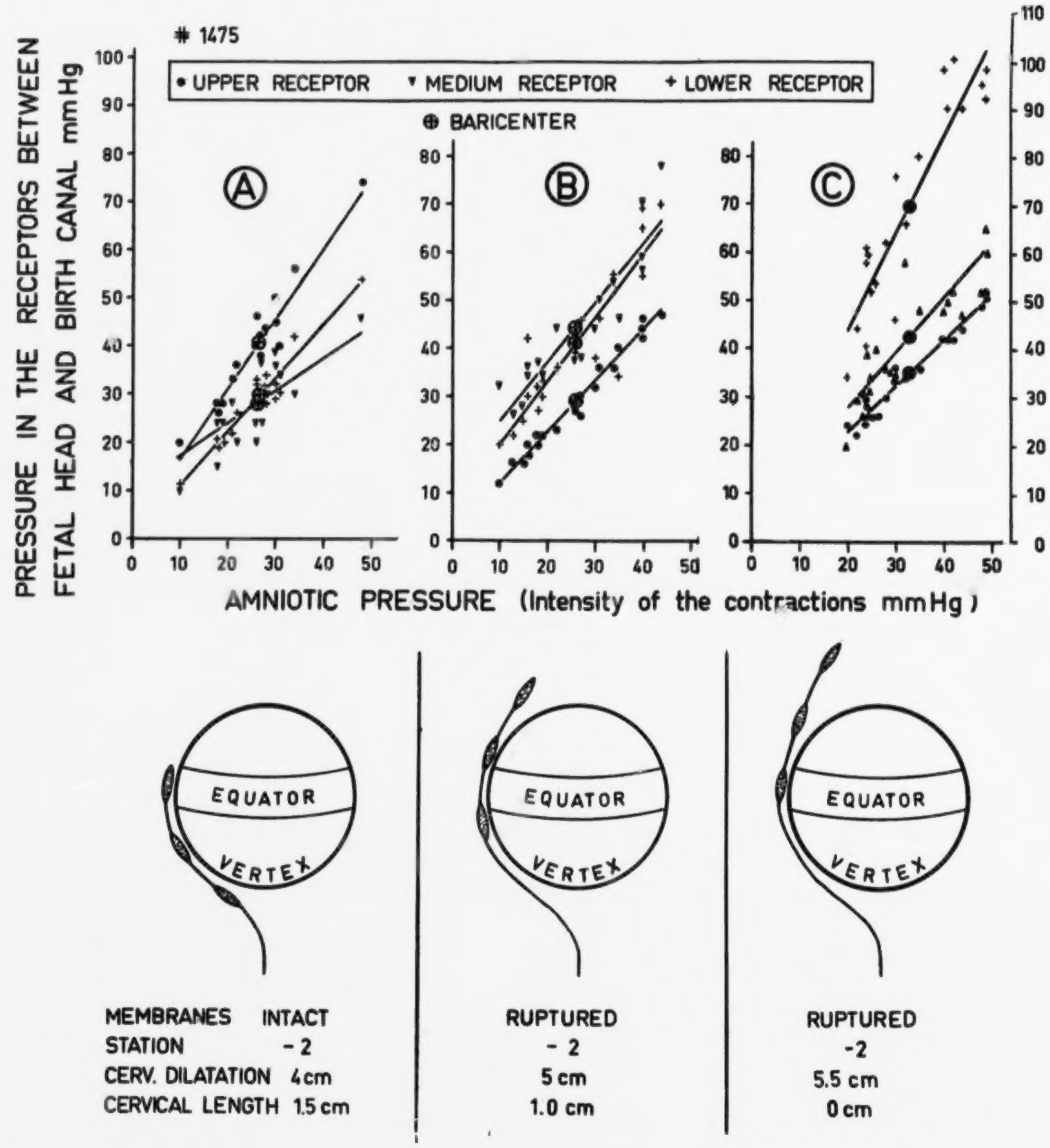


Figure 3

labor in which the cervical dilatation and the station remained unchanged, a direct linear relationship was found (figs. 3 and 6). The correlation coefficient (r) had very high values (0.93 to 0.97 in fig. 6).

When the receptors changed their position in relation to the fetal head (as a consequence of the progress of cervical dilatation or of the station) a new linear correlation was established; the value of the intercept and of the regression coefficient changed depending on the new position of the receptor relative to the fetal head.

When a cephalic receptor was distant (more than 2 cm) from the equator of the fetal head, the regression coefficient was close to the unit and the intercept was close to zero; the pressure recorded by that receptor was very similar to that in the amniotic cavity. This is the condition of the lower and medium receptors

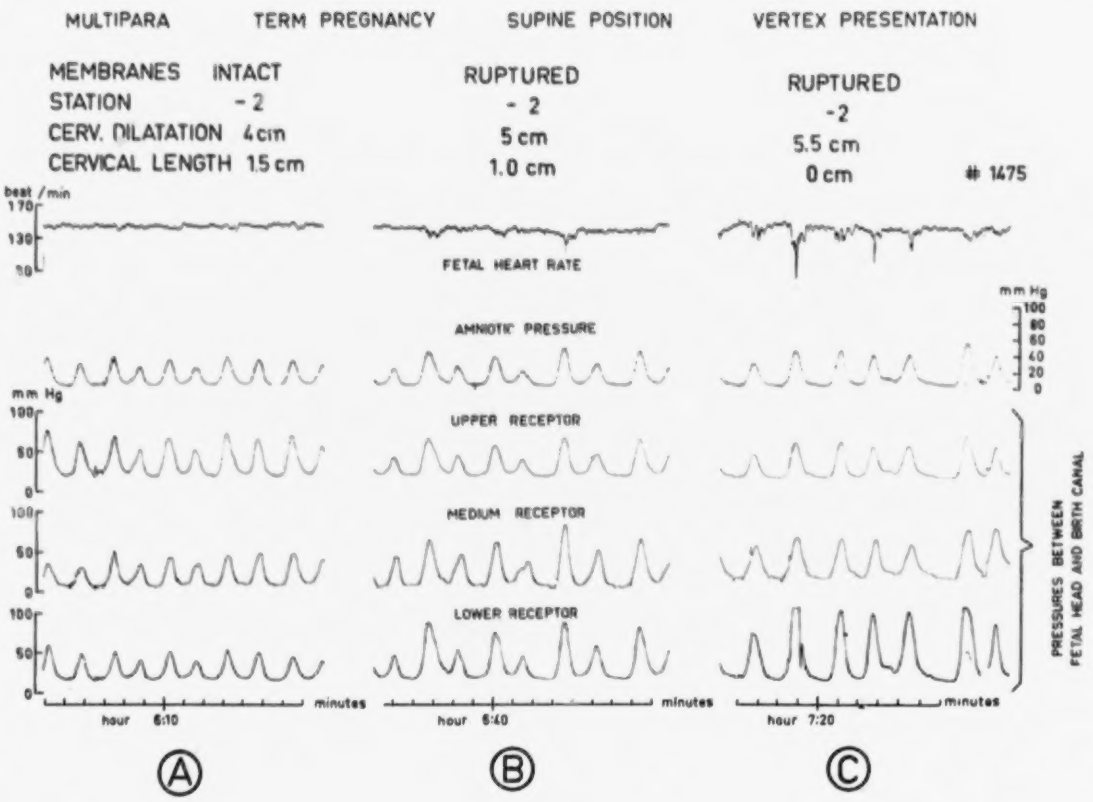


Figure 4

in sections A and the upper and medium receptors in sections C of figs. 3 and 5.

When a receptor moved closer to the equator of the fetal head, the pressure at the peak of the uterine contraction was much higher than in the amniotic pressure record. This is the condition prevailing in the upper receptor in Section A and in the lower receptor in Section C of figs. 3 and 4. The regression coefficient became significantly greater than 1; in some instances it reached values as high as 2.5. The highest values of the regression coefficient were usually obtained after rupture of the membranes (lower receptor in section C of figs. 3 and 4). The progress of labor was also associated with augmentation of the ratio between the cephalic and amniotic pressures (figs. 3 and 4).

In fig. 6 the regression line no. I corresponds to all the pressure measurements made with several cephalic receptors when they were distant from the equator. Regression line no. 2 corresponds to receptors placed near the equator after rupture of the membranes and at the equator before rupture of membranes. Regression line no. 3 corresponds to a receptor located at the equator of the fetal head after the rupture of membranes.

Figure 6 shows that the regression coefficients were significantly higher for the receptors near the equator of the fetal head than for those distant from the equator (compare regression line 1 with 2 and 3). It also shows that the pressures recorded at the receptors near the equator of the fetal head were higher when the membranes were ruptured than before (compare regression lines 2 and 3).

If the fetus was not suffering from systemic hypoxia and acidosis, uterine contractions caused no changes in FHR as long as the pressure received by the

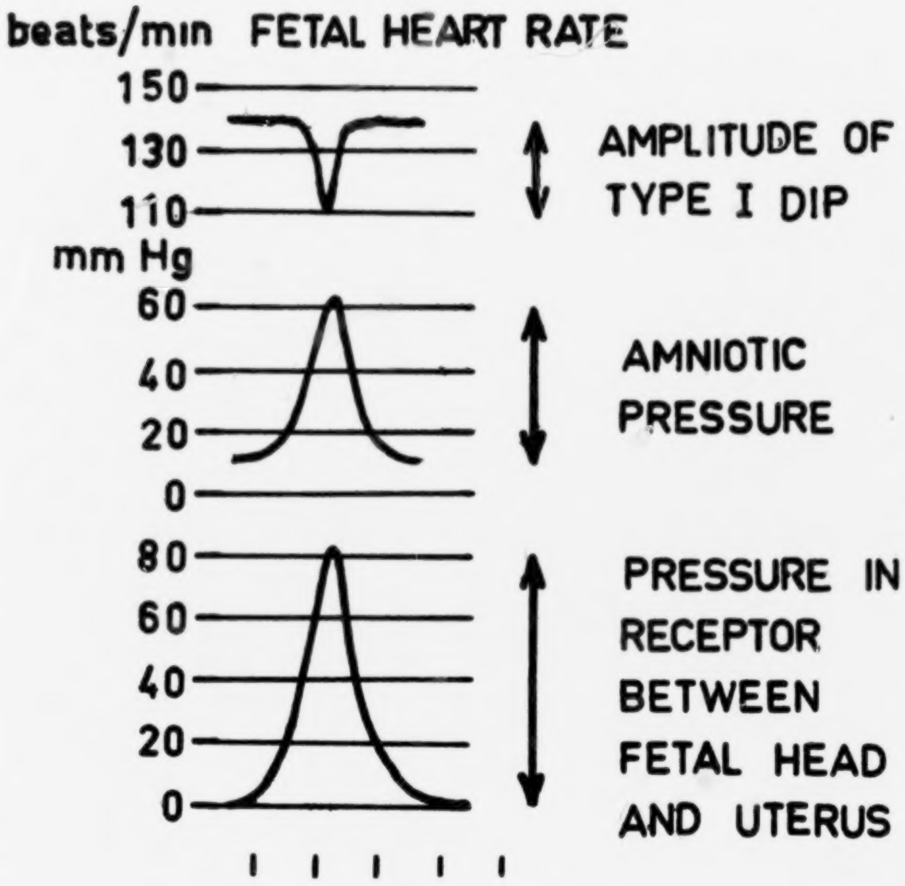


Figure 5

fetal head during each uterine contraction was not higher than the amniotic pressure (fig. 4A). Under these conditions the FHR tracing showed the normal "rapid" oscillations, the baseline was close to 140 beats/min, and no FHR changes correlated with the contractions were seen (i.e., dips I were absent).

When the compression exerted on the fetal head by one uterine contraction was significantly higher than that on the amniotic cavity, a transient fall ("dip I") occurred in FHR (fig. 4, B and C). The greater the pressure exerted by the uterine contraction on the fetal head, the larger the amplitude of the corresponding dip I in FHR (compare sections B and C in fig. 3).

Figure 7 shows the direct linear relationship present between the amplitude of dips I and the pressure recorded in the cephalic receptors at the peak of the corresponding uterine contraction. When this pressure was higher than 50 mm Hg, almost every contraction caused a dip I in FHR tracing.

Discussion

Our results confirm Lindgren's report that under given conditions the pressure exerted by uterine contractions on the receptors placed between the fetal head and the uterine wall may be much higher than the pressure in the amniotic cavity, and that the receptor at the equator of the fetal head records the highest pressure.

The ratio (pressure in cephalic receptor/amniotic pressure) is much higher

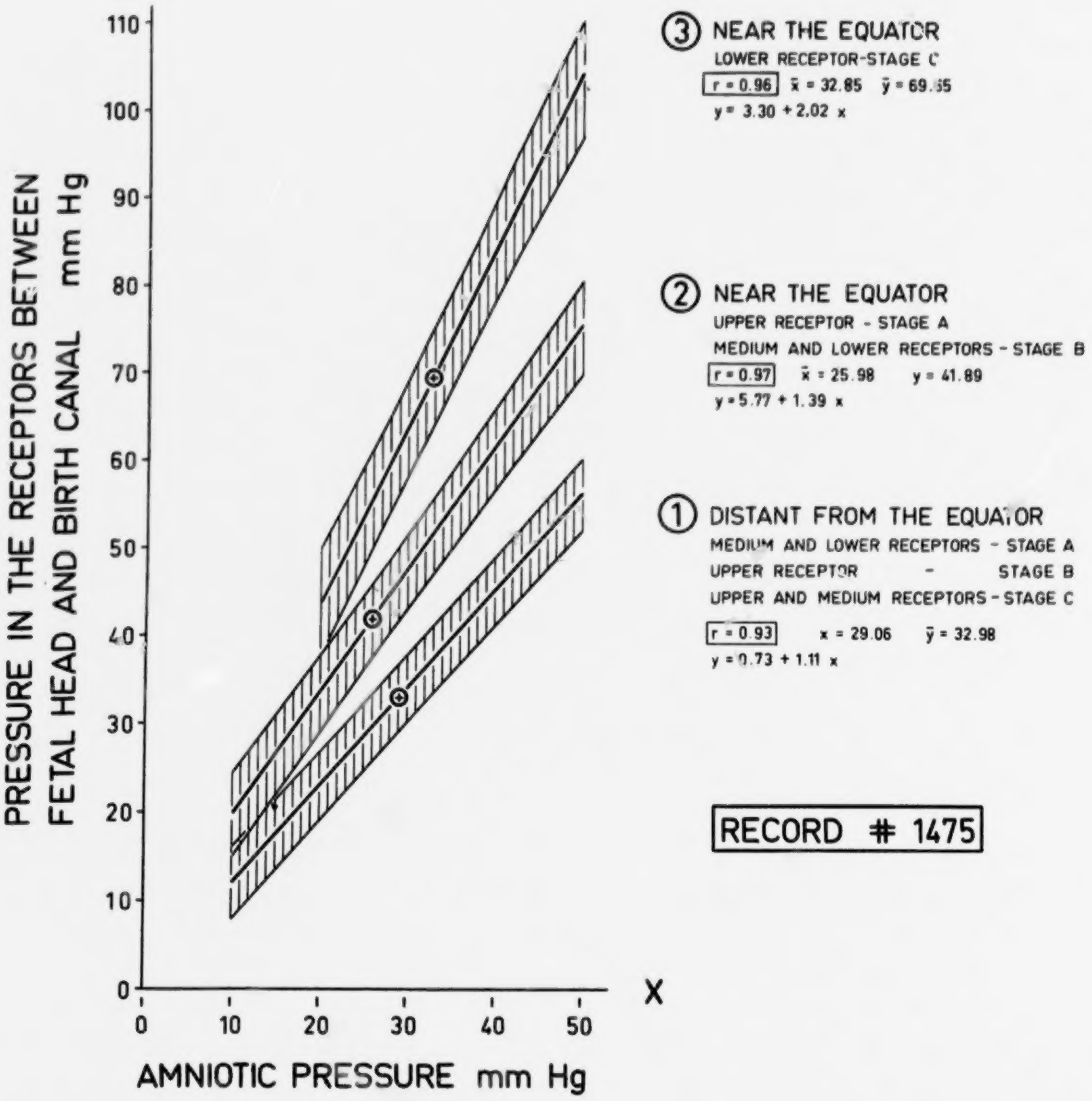


Figure 6

in Lindgren's results than in those reported here, even for similar obstetrical conditions (fig. 8).

Whereas we found a linear relationship between the pressure in the cephalic receptors and the amniotic pressure, Lindgren found that when the amniotic pressure increases beyond a certain limit, the linear relation is lost (fig. 8), since the pressure in the cephalic receptor does not augment accordingly. These discrepancies may be due to differences in the type of cephalic pressure receptors employed.

The correlation between the pressure in the cephalic receptors and the amplitude of dips I (fig. 7) is in agreement with the hypothesis that these transient falls in FHR are caused by strong compression exerted by the uterine contraction on the fetal head. To cause a dip I, the cephalic compression should be greater than 40 mm Hg and higher than the pressure rise in the amniotic cavity.

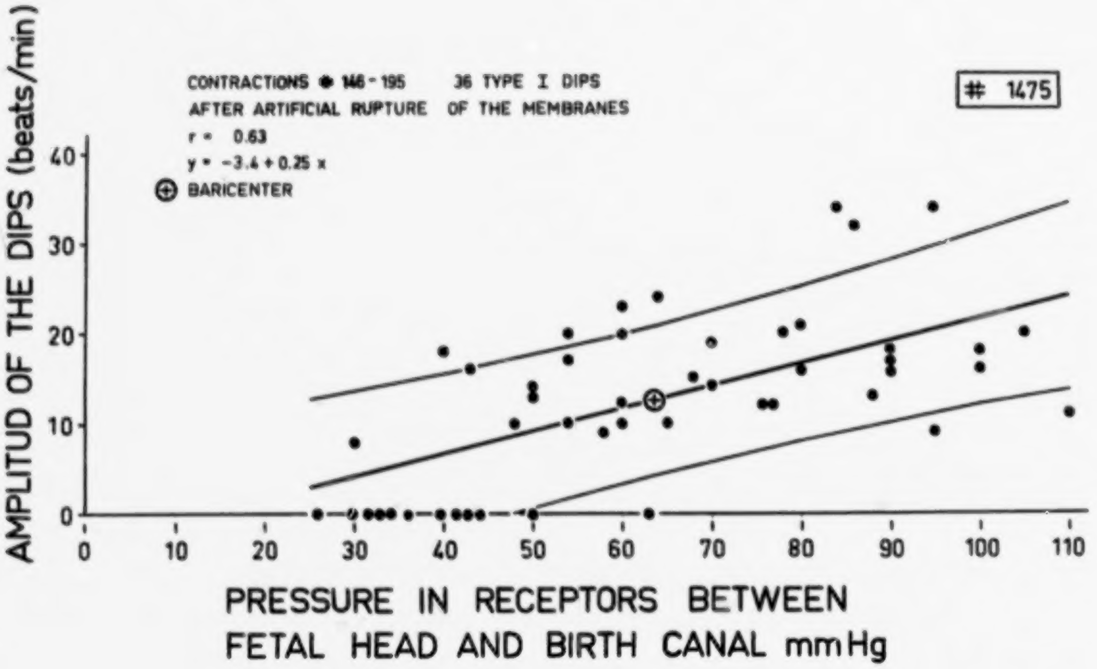


Figure 7

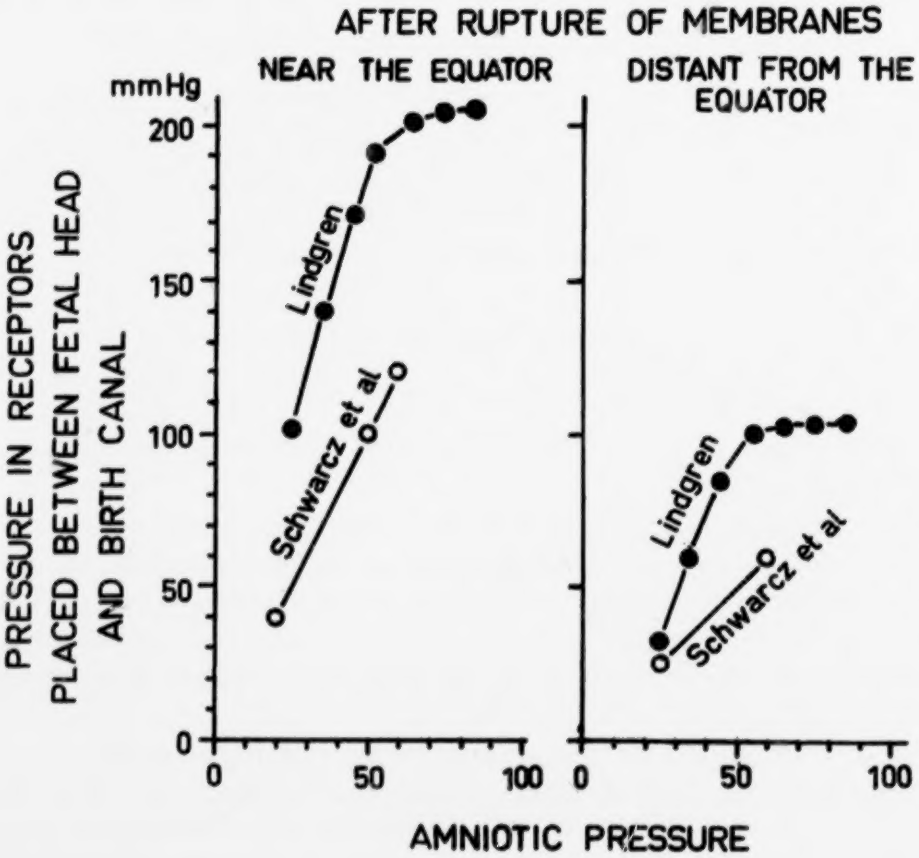


Figure 8

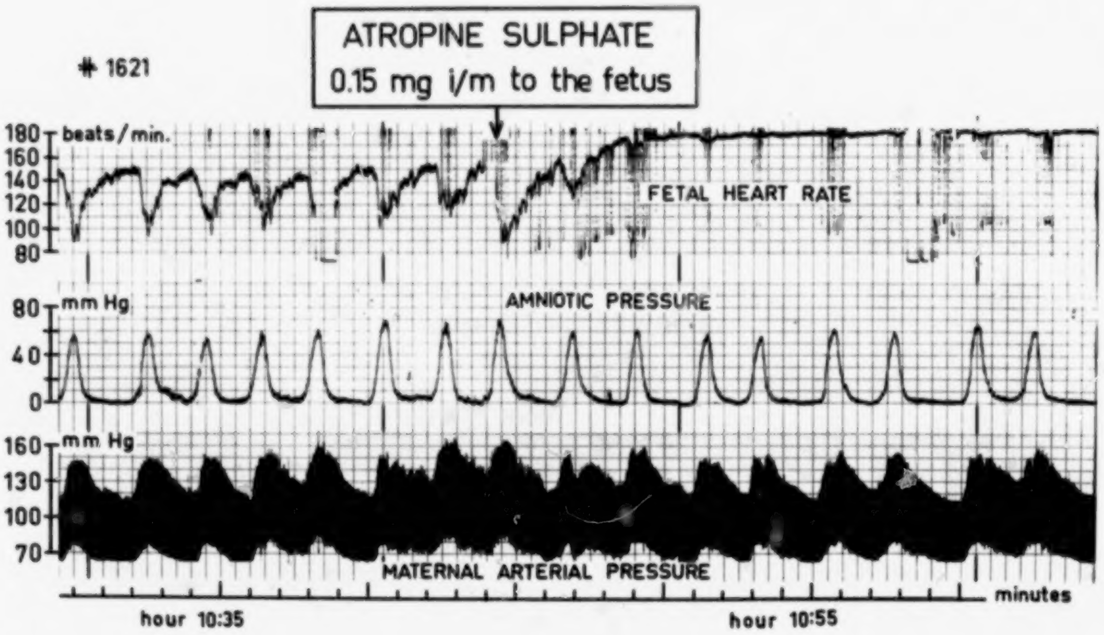


Figure 9

The complete disappearance of type I dips after fetal atropinization (fig. 9) is in agreement with the hypothesis that increased vagal tone is the mechanism involved in the pathogenesis of dips I.

Cephalic compression could produce increased intracranial pressure with the consequent reduction of cerebral blood flow. The resulting hypoxia and hypercapnia of the CNS would stimulate the vagus center.

A transient cerebral ischemia can also explain the changes observed in the fetal EEG (slow waves of high voltage) during the peak of strong uterine contractions producing dips I.

The fact that the compression on the equatorial zone of the fetal head is stronger than on the other areas should cause a deformation (moulding) of the head.

DISCUSSION

Dr. Churchill: I am intrigued by these observations and wonder if you've had a chance to follow even briefly some of these babies who've had seizures shortly after birth. Though we don't have precise data, some of these infants will show no other abnormality than an intermittent sharp wave, and no other abnormalities on examination. As time goes on, we follow the infant and it develops normally and has no more seizures.

On the other hand, we have seen infants who have a similar EEG, but no data revealing grossly abnormal labor, who immediately seem not to function too well, for example, being without good visual pursuit. These go on to develop slowly and have recurrent seizures and worsening of the EEG.

Dr. Caldeyro: We don't know yet if a baby showing these low waves behaves differently from the other infants. It is the type of information that we plan to collect in the future.

Dr. Engel: First, I think that Dr. Caldeyro should be congratulated on this obviously very difficult and most fascinating work. Insofar as the infant EEG's are concerned, I personally think that it would be a bit safer at this point to simply describe the EEG changes seen as a frequency shift. It's very, very difficult to identify seizure discharges in neonatal EEG's with any confidence. I don't know if anybody can do it. The safest way to identify them is to observe a seizure going on at the time you're looking at what you think is aberrant electrical activity.

All sorts of transient patterns occur in the infant EEG, most of which are probably of no significance. They're very common, for example, at 30 to 33 weeks of conceptual age. You will even see them in a small percentage of full-term apparently normal babies. During actual seizures, EEG's vary a great deal during the neonatal period. Some infants show only semi-rhythmic, arrhythmic slow waves with no spike components whatever. Very rapid spike components are relatively uncommon. The payoff here, I think, will be the follow-up to observe whether or not there are differences in children who show these phenomena during your recordings.

Participant: I'd just like to ask whether you have any observations on pituitrin–induced labor?

Dr. Caldeyro: If properly induced, the contractions are very much like those of normal labor. The main difference lies in the fact that when you induce labor by infusion, the lower part of the uterus may not be ripe. If the lower part does not yield easily, then there is an important difference. Instead of needing 100 or 150 contractions to accomplish labor, you will need 400, 500, 600 or more contractions, and this is what produces at the end, depressed babies and perhaps damaged babies.

We have become much more conservative. Ten years ago we used to consider induction of labor as perfectly safe, but today we only do it when it is specially indicated, and we cease producing contractions as soon as we see any changes in the heart rate. When you have more than 300 or 400 contractions, even the most normal babies start to show signs of distress.

REFERENCES

Arellano-Hernández, G., et al. Efectos de la compresión de la cabeza fetal, de la fontanela y del cordón umbilical sobre la Frecuencia Cardiaca Fetal. *IV Cong. Mex. Ginec y Obst. II:* 433, June 1963.

Caldeyro-Barcia, R. Estudio de la anoxia fetal intrauterina mediante el ECG fetal y el registro continuo de la Frecuencia cardiaca fetal. *III Congr. Lat. Am. Obst. Ginec. 2:* 388, June 1958.

Caldeyro-Barcia, R., and Alvarez, H. Abnormal uterine action in labour. *J. Obstet. Gynaec. Brit. Comm. 59:* 646–656, Oct. 1952.

Caldeyro-Barcia, R., et al. Significado de los cambios registrados en la Frecuencia Cardiaca Fetal durante el parto. *IV Congr. Mex. Ginec. y Obst. 2:* 15, June 1963.

Caldeyro-Barcia, R., et al. Control of human fetal heart rate during labor. In: *International Symposium on the Heart and Circulation in the Newborn and Infant.* D. E. Cassels (ed.), Grune & Stratton, New York, 1966, pp. 7–36.

Chung, F., Hon, E. H. The electronic evaluation of fetal heart rate. I. With pressure on the fetal skull. *Obstet. Gynec. 13:* 633–640, June 1959.

Figueroa-Longo, J. G., et al. Fetal electrocardiogram at term labor obtained with subcutaneous fetal electrodes. *Amer. J. Obstet. Gynec. 96*: 556–564, Oct. 15, 1966.

Garcia Austt, R., Ruggia, R., and Caldeyro-Barcia, R. Effects of intrapartum uterine contractions on the EEG of the human fetus. In: *Physical Trauma as an Etiological Agent in Mental Retardation.* C. Angle (ed.) Fourth Multidisciplinary Conference on the Etiology of Mental Retardation.

Hon, E. H. Observations on "pathologic" fetal bradycardia. *Amer. J. Obstet. Gynec. 77:* 1084–1099, May 1959.

Hon, E. H., and Quilligan, E. J. The classification of fetal heart rate. II. A revised working classification. *Conn. Med. 31:* 779–784, Nov. 1967.

Ingelman-Sundberg, A., and Lindgren, L. Intra-uterine measurement of pressure during labour. *J. Obstet. Gynaec. Brit. Comm. 62:* 629–635, Aug. 1955.

Lindgren, L. The lower parts of the uterus during the first stage of labour in occipito-anterior vertex presentation; studies by means of intrauterine tokography. *Acta Obstet. Gynec. Scand. 34:* 1–79 (Suppl. 2), 1955.

Lindgren, L. The effect of rupture of the membranes upon the mechanism of labour. *Acta Obstet. Gynec. Scand. 38:* 211–226, 1959.

Méndez-Bauer, C., et al. Effects of atropine on the heart rate of the human fetus during labor. *Amer. J. Obstet. Gynec. 85:* 1033–1053, April 15, 1963.

Schwarcz, R., and Salaber, J. *Semana Médica 23:* 5, 1927.

Schwarcz, R., et al. *IV Congr. Mundial Ginec y Obst.*, 308. Mar del Plata, Argentina, 1964.

Strada Sáenz, G., et al. Presión recibida por la cabeza fetal durante las contracciones uterinas del trabajo de parto y su relación con la frecuencia cardiaca fetal. *IV Congr. Urug. Ginecotocol II:* 903, 1964.

NEWBORN CEREBRAL TRAUMA

John A. Churchill, M.D.
Section on Pediatric Neurology
Perinatal Research Branch
National Institute of Neurological Diseases and Stroke
Bethesda, Maryland

Intrapartum and neonatal death can occur from mechanical trauma to the brain during birth. The literature is replete with pathologic reports of cerebral lesions attending mechanically stressful accidents and modes of delivery. (Holland; Brouwer; Schwartz; Norman). Doctor Malamud has demonstrated some of these lesions today.

Doctor Russell has just reported that 6.2 percent of his series of newborns studied at autopsy had traumatic lesions in the brain. This represents 0.2 percent of all births in his study. His value is less by a factor of six than the proportion of new born brains showing traumatic lesions in three investigations prior to 1935 (Warwick 1919, 1921; Pierson; Irving). The incidence of trauma as the cause of perinatal death was estimated by Irving in 1930 to be 2 percent. Can this great reduction in lethal traumatic births be attributed to improved obstetric skill?

On *a priori* grounds one considers that factors such as birth trauma, which can be lethal, may produce morbidity in survivors. But the evidence is less direct and less compelling that intrapartum trauma results in central nervous system dysfunction.

Roberts showed that more than 10 percent of infants suffer trauma in the perinatal period, but only a small fraction of these show conspicuous neurologic deficits later. One is led to wonder how bloody the cerebrospinal fluid (CSF) must be to indicate trauma and whether the spinal puncture itself is the trauma.

Doctors Clifford and Drorbaugh suggest that 16 percent of conspicuously impaired children, or 0.12 percent of their total number of live births, were judged neonatally to have suffered intrapartum trauma. If trauma causes this number of obviously impaired children, one must entertain the idea that many others have mild neurologic deficits and that deficits undetectable by present-day instruments may occur in even more. Indeed, serious thought should be given to the postulate that some brain damage results in the course of every birth.

Doctor Russell has reported that breech delivery in high birth weight infants is associated with deficits on psychological tests. Apgar ratings are depressed in breech births. To what extent is the IQ deficit a result of asphyxia rather than of mechanical trauma?

Doctor Rosenbaum's report on breech delivery differs in some methodologic details from Dr. Russell's. Doctor Rosenbaum reports only a slight trend toward a difference in Binet IQ between breech and LOA births. Perhaps the differences in the findings of the two studies are to be found in the differences of IQ test used, other characteristics of the populations, or numbers of cases. One would expect breech delivery to be associated with depressed IQ and negative or minimal findings must be examined in critical detail.

Doctors Drorbaugh and Clifford cited occiput posterior presentation (OP), cephalopelvic disproportion, and prolonged labor in their series of ostensibly brain injured cases. Occiput posterior births were found to be associated with neuropsychologic deficits as reflected in the Binet score in Dr. Rosenbaum's study. The head in OP births is often rotated through an arc of 45° more than in the OA head presentations. These mechanical adversities marked by distortion and elongation of the skull may be associated with brain injury (Ehrenfest, Greenwood).

Cephalopelvic disproportion was implicated by Drs. Drorbaugh and Clifford as a cause of brain damage. Data presented by Dr. Willerman showed that women with smaller pelvic dimensions had children of IQ significantly lower than those of children whose mothers had more ample pelvic capacities.

The findings suggest that the fetal brain may be compressed, distorted and injured sufficiently in the passage through the pelvic canal to impair intellectual functions later in life. Measurements of intrauterine pressure and force exerted on the fetal head during delivery have been made by Dr. Caldeyro-Barcia. He has shown that the magnitude of force during uterine contraction is related to fetal heart rate, an effect attributable in part to increased intracranial pressure. Perhaps of greater importance are his preliminary findings of an association between pressure rises during uterine contractions and the appearance of slow waves in the EEG of the as-yet-undelivered infant. Doctor Caldeyro-Barcia plans to record fetal EEGs in such a way that interhemispheric differences in slow wave production could be identified.

Not only is knowledge incomplete regarding whether central nervous system (CNS) dysfunction results from intrapartum trauma, it is even more deficient regarding what particular kinds of cerebral dysfunctions result from birth trauma. In regard to the specific topic of this symposium, whether mental deficit results from trauma at birth, the record has been almost bare.

Ford has postulated that the outstanding result of trauma at birth is hemiplegia, which is often accompanied by convulsive seizures. Earle, Baldwin and Penfield showed experimentally how the temporal lobe could be injured at birth, the injury resulting in epileptogenic lesions.

In an effort to carry forward their work on the etiology of hemiplegic cerebral palsy, I formulated the spatial theory of differential cerebral impairment, which holds that, given suboptimal conditions of cephalopelvic fit and forces of labor, injury to the brain occurs. Traumatic forces do not act diffusely or equally throughout the brain; rather focal regions of maximal injury develop. The region of the brain in greatest jeopardy is determined by the spatial orientations of the infant head as it descends through the maternal pelvis. One hypothesis to test the theory was that children with focal motor epilepsy would be borne LOA if the epileptogenic focus was located primarily in one hemisphere; wheras the ROA position at birth would be found in children with foci in the other cerebral hemisphere.

The hypothesis was confirmed by direct study and subsequently reconfirmed in a study of hemiplegic cerebral palsy (Churchill 1966, 1968). The association found was opposite to that which would be predicted on *a priori* grounds; that is, left-sided lesions were associated with ROA births, and conversely, right-sided lesions with LOA births. Electroencephalographic studies, both on newborns and on older children, also support the theory (Churchill, *et al,* 1966; Churchill and Rodin).

What is important, not only as a topic here but also relevant to both the classic problem of cerebral dominance and that of differences in intellectual attributes among people, is whether differential impairment of cerebral function as related to birth holds true for higher mental functions.

Doctor Willerman has undertaken this difficult task and has shown in several separate studies findings consistent with the theory (Churchill, *et al,* 1968). Procedureal problems remain to be clarified in more detail. For example, do ROA-born babies differ from LOA-born babies before birth ? Is ROA-birth more traumatizing than LOA? Do the mothers with LOA delivery differ somehow in other characteristics from ROA-presenting mothers? The data so far gathered by Dr. Willerman suggest that none of these factors account for the psychometric differences between LOA- and ROA-born children.

To accept the findings, one must discard the prevailing postulate that the cerebral hemispheres of the newborn are equipotential for the development of verbal functions and accept the postulate that verbal functions usually develop in the left hemisphere because of genetically-determined structural differences between the hemispheres. Geschwind has recently presented exciting evidence that anatomic differences are indeed present between the left and right halves of the cerebrum.

REFERENCES

BROUWER, B.: Traumatic changes in the brain after spontaneous delivery at full term. *Proc. Roy. Soc. Med. 42: 603–608, (Aug) 1949.*

CHURCHILL, J. A.: A study of hemiplegic cerebral palsy. *Develop. Med. Child. Neurol. 10: 453–460 (Aug) 1968.*

CHURCHILL, J. A.: On the origin of focal motor epilepsy. *Neurology 16: 49–58 (Jan) 1966.*

CHURCHILL, J. A., GRISELL, J., and DARNLEY, J. D.: Rhythmic activity in the EEG of newborns. *Electroenceph. Clin. Neurophysiol. 21: 131–139, (Aug) 1966.*

CHURCHILL, J. A., and RODIN, E. A.: Asymmetry of alpha activity in children. *Develop. Med. Child Neurol, 10: 77–81, (Feb) 1968.*

CHURCHILL, J. A. et al.: Effect of head position at birth on WISC verbal and performance IQ *Psychol. Rep. 23: 495–498, 1968.*

EARLE, K. M., BALDWIN, M., and PENFIELD, W.: Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. *Arch. Neurol. Psychiat. 69: 27–42, (Jan) 1953*

EHRENFEST, H.: *Birth Injuries of The Child.* New York: Appleton and Co., 1922.

FORD, F. R.: *Diseases of the Nervous System in Infancy, Childhood and Adolescence.* ed 5, Springfield, Illinois: Charles C Thomas, Publisher, 1966.

GESCHWIND, N.: Human brain: left-right asymmetries in temporal speech region. *Science 161: 186–187, (July 12) 1968.*

GREENWOOD, W. O.: The moulding of the foetal head and its consequences. *J. Obstet. Gynaec. Brit Comm 31: 611–621, 1924.*

Holland, E.: Cranial stress in foetus during labor and effects of excessive stress on intracranial contents. *J. Obstet. Gynaec. Brit. Comm. 29: 549–571, 1922.*

Irving, F .C.: Obstetrical aspects of intracranial hemorrhage. *New Eng. J. Med. 203: 499–502, (Sept 11) 1930.*

Malamud, N.: Sequelae of perinatal trauma. *J. Neuropath. Exp. Neurol. 18: 141–155, (Jan) 1959.*

Norman, R.: Etat marbré of the thalamus following birth injury. *Brain 72: 83–88 (March) 1949.*

Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization; A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures.* Springfield, Illinois; Charles C Thomas, 1941.

Pierson, R. N.: Spinal and cranial injuries of baby in breech deliveries. *Surg. Gynec. Obstet. 37: 802–815, (Dec) 1923.*

Roberts, M. H.: The spinal fluid in the newborn with especial reference to intracranial hemorrhage. *JAMA 85: 500–503, (Aug 15) 1925.*

Schwartz, P.: Birth injuries of the newborn. Morphology, pathogenesis, clinical pathology and prevention of birth injuries of the newborn. *Arch. Pediat. 73: 429–450, (Dec) 1956.*

Spencer, H. R.: On visceral haemorrhages in stillborn children analysis of 130 autopsies, being a contribution to the causation study of the still birth. *Trans. Obstet. Soc. London 33: 203–300, 1892.*

Warwick, M.: Cerebral hemorrhage in the newborn. *Amer. J. Med. Sci. 158: 95. (July 19) 1919.*

Warwick, M.: Necropsy findings in newborn infants. *Amer. J. Dis. Child. 21: 448, (May) 1921.*

SESSION IV

Special Studies of the Developing Brain

Session Chairman: Ellsworth C. Alvord, Jr., M.D.

TRAUMA OF LABOR

Edward H. Hon, M.D.
Department of Obstetrics and Gynecology
Yale University School of Medicine
New Haven, Connecticut

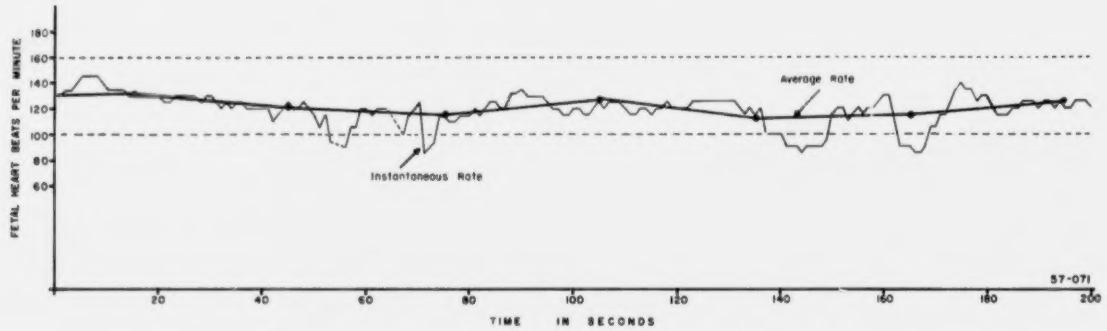
In the absence of hard data on the effects of anoxia, trauma, and drugs on the human fetus, it will be difficult for the pediatrician and neurologist to correlate obstetrical findings with later infant growth and development. The obstetrical records and data we have on the fetus are just not good enough. The present techniques of acquiring and recording data during labor and delivery are relatively inaccurate. In 13 years of observing clinical obstetrics, our research team has found that there is little resemblance between the clinical record made by the obstetrician and our research records of fetal heart rate (FHR), electrocardiogram (FECG), and uterine pressures.

Another significant problem is the absence of a hard reference point in defining clinical fetal distress. We can only assess fetal distress, and the success of any therapeutic measures employed, in the terms of immediate neonatal condition and later infant growth and development. The techniques for assessment of the neonate and infant also need further development.

Our research group is biophysical, in orientation; our approach to labor from a research standpoint is fundamentally that of biophysicists. The FHR we study is not the FHR as determined clinically with a stethoscope in the interval between contractions. We are concerned with the beat-to-beat difference in FHR and the moment-by-moment presentation of its changes.

Figure 1 is a comparison of the instantaneous and averaged FHR graphed from the same FECG data. The heavy line joining the series of dots is the FHR averaged over a period of 30 seconds, and the irregular, thinner line is the instantaneous FHR from which the averaged FHR was obtained. It is quite evident that there is a great loss of FHR detail when an averaging technique is used. We believe that the interval difference between successive fetal heart beats is a very important measurement, for it appears to reflect the integrity of the nervous control of the heart. Precise techniques for a computation of the instantaneous FHR are therefore important in this type of study.

This investigation was supported in part by Research Grants HD 01467-03 and 5K03 HD 18, 295-06 from the National Institute of Child Health and Human Development and Computer Grant FR 3 from the Health Sciences Computing Facility, University of California at Los Angeles.



COMPARISON OF INSTANTANEOUS AND AVERAGE FETAL HEART RATES

FIGURE 1.—The fetal heart rate (FHR) averaged over 30-second intervals as compared with the instantaneous rate, based on the interval between successive beats.

Figure 2 shows in detail how the instantaneous FHR is computed with an instantaneous fetal cardiotachometer whose electronic circuits measure the interval t between successive triggers created by passing the FECG through a narrow band-pass filter, shown in the upper trace of fig. 2. The sucessive intervalts t_1, t_2, ... t_n are measured, and for each interval a potential E, inversely proportional to t, is computed. The series of resulting potentials may be displayed on a meter, oscilloscope, or other recorder, or may be fed directly into a computer.

For this type of FHR study a clean signal source for the cardiotachometer is important. Our technique for clinical monitoring, a little different from those used in South America, is illustrated in fig. 3. We use a transcervical catheter rather than a transabdominal one; the electrode is attached directly to the fetal presenting part, rather than having it pass through the abdominal wall of the mother into the fetal buttocks.

Effects of labor. The traditional obstetrical concept of labor is that it is a mechanism for extruding the fetus from the uterus, thus, progress in labor is evaluated in terms of cervical dilatation and fetal descent. While this narrow concept may be valid from a maternal standpoint, from the fetal standpoint each uterine contraction represents a recurring stress.

Figure 4 indicates that the mechanical energy of a uterine contraction may be applied to the umbilical cord (causing partial or complete occlusion), to the fetus directly (usually the vertex), and to the fetus indirectly by impeding arterial and venous flow to and from the intervillous space of the placenta (the vascular supply to this space must run the gauntlet of the contracting myometrium). Thus labor itself may be a significant etiologic factor in perinatal morbidity and mortality.

While the direct effects of uterine contractions are obvious, the indirect effects of each uterine contraction on intervillous space blood flow are less easy to visualize. Figure 5, taken from the studies with pregnant rhesus monkeys of Dr. Frank Greiss, illustrates the effect of intrauterine pressure (IUP) on uterine blood flow (UBF). The upper series of traces shows that each uterine contraction is associated with an alteration in uterine blood flow reflecting the changes in the shape of the intrauterine pressure curve. In the lower series of traces,

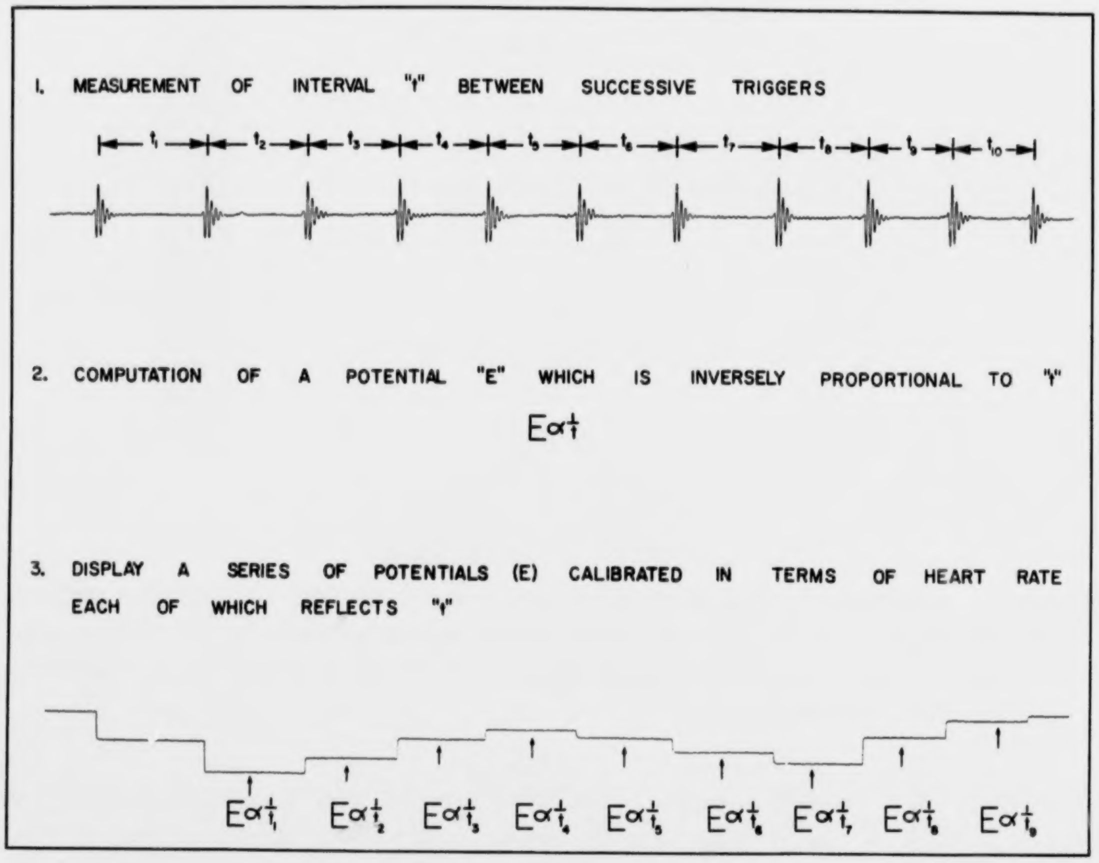

1. MEASUREMENT OF INTERVAL "t" BETWEEN SUCCESSIVE TRIGGERS
t_1 t_2 t_3 t_4 t_5 t_6 t_7 t_8 t_9 t_{10}
2. COMPUTATION OF A POTENTIAL "E" WHICH IS INVERSELY PROPORTIONAL TO "t"
$E \propto \frac{1}{t}$
3. DISPLAY A SERIES OF POTENTIALS (E) CALIBRATED IN TERMS OF HEART RATE EACH OF WHICH REFLECTS "t"
$E \propto \frac{1}{t_1}$ $E \propto \frac{1}{t_2}$ $E \propto \frac{1}{t_3}$ $E \propto \frac{1}{t_4}$ $E \propto \frac{1}{t_5}$ $E \propto \frac{1}{t_6}$ $E \propto \frac{1}{t_7}$ $E \propto \frac{1}{t_8}$ $E \propto \frac{1}{t_9}$

Figure 2.—Computation of the instantaneous FHR by measurement of the interval t between successive triggers (1) created by passing the fetal ECG (FECG) through a narrow band-pass filter. The successive intervals t_1, t_2, . . . t_n are measured and a potential E, inversely proprotional to t is computed.

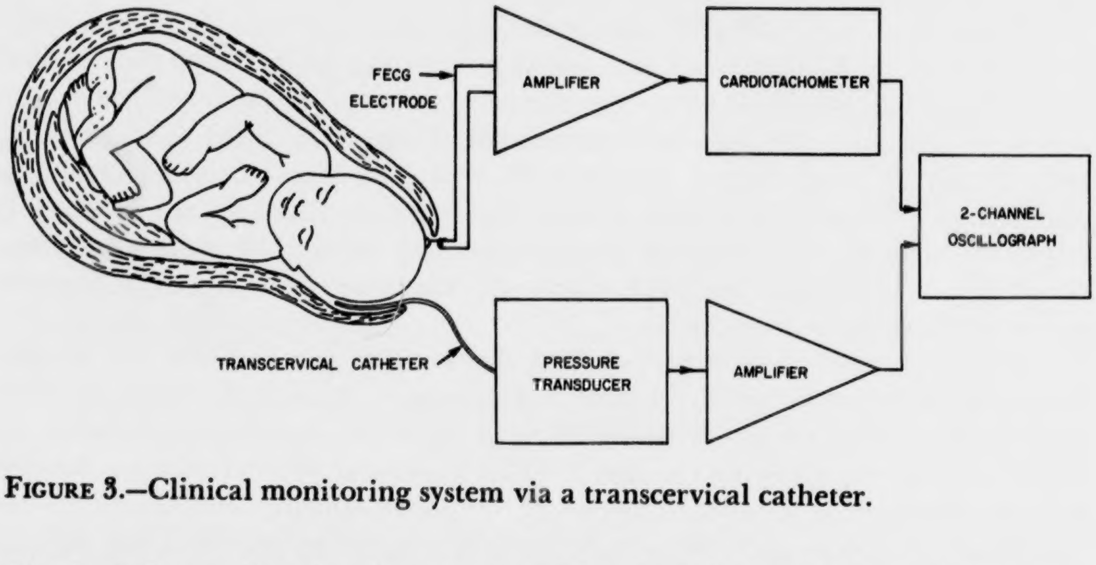

FECG ELECTRODE
AMPLIFIER
CARDIOTACHOMETER
2-CHANNEL OSCILLOGRAPH
TRANSCERVICAL CATHETER
PRESSURE TRANSDUCER
AMPLIFIER

Figure 3.—Clinical monitoring system via a transcervical catheter.

where uterine activity has been increased by the infusion of Syntocinon, the increase in frequency and amplitude of the contractions is reflected by a concomitant decrease in uterine blood flow. As the Syntocinon dosage is increased two-

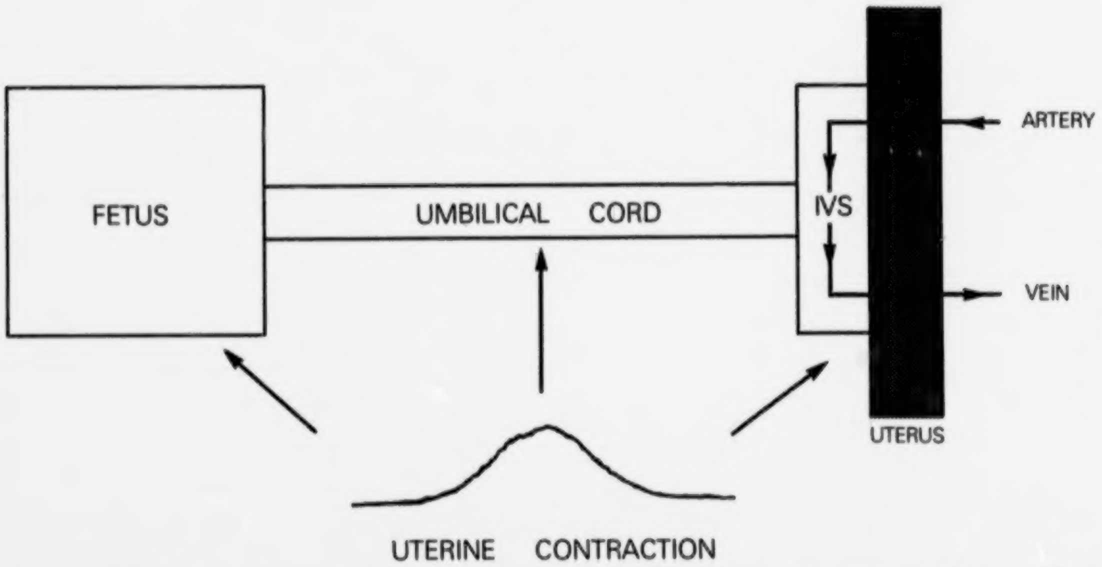


FIGURE 4.—Schematic representation of how the mechanical energy of a uterine contraction may be applied to the fetus (usually the vertex), to the cord (with partial or complete occlusion), or indirectly to the fetus by impeding intervillous blood flow.

fold, there is a marked increase in uterine activity and a similar marked decrease in uterine blood flow. Every uterine contraction decreases intervillous space blood flow to some extent and, consequently, decreases maternal-fetal exchange. In circumstances where the fetal margin of reserve is low, the addition of this repetitive stress may be sufficient to compromise fetal well-being. It is important, therefore, during labor and delivery, to evaluate the fetus during uterine contractions when the greatest stress is being applied. If FHR is used for the evaluation of fetal well-being, FHR changes should be recorded during contractions as well as during the intervals between contractions.

Figure 6, a record of FHR and uterine contractions (UC), shows that FHR does not slow with all contractions and that it is not normal for this to occur. FHR alterations associated with contractions are labeled periodic FHR changes, and the FHR alterations between the periodic changes are called baseline FHR. Periodic FHR changes include rises in FHR that have been labeled accelerations and falls in FHR that have been labeled decelerations. Rises or falls in baseline FHR are labeled tachycardia or bradycardia, respectively, to distinguish them from rises or falls in periodic FHR. Clinically, the most important FHR patterns appear to be those of deceleration.

Figure 7 shows three different FHR deceleration patterns that are consistently associated with specific clinical circumstances. Record A shows an FHR pattern of uniform shape where the onset of the FHR deceleration occurs *early* in the contracting phase of the uterus. This particular type of pattern, labeled early deceleration, is thought to be due to compression of the fetal vertex. In our experience, this type of FHR pattern has not been associated with any clinical problems but many more patients need to be studied.

Record B shows another FHR pattern of uniform shape that, like A, reflects the shape of the associated uterine contraction curve. In this instance, however,

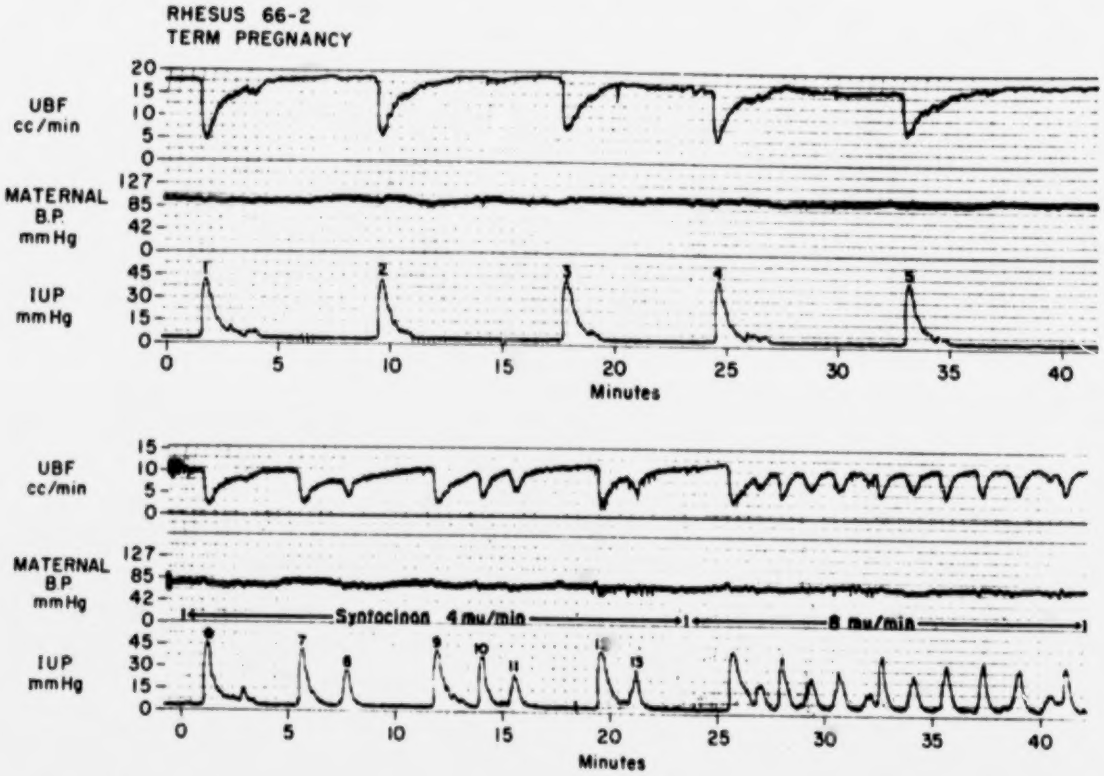


FIGURE 5.—Effect of intrauterine pressure (IUP) on uterine blood flow (UBF).

the onset of the deceleration occurs *late* in the contracting phase of the uterus and has been labeled late deceleration. This particular pattern is thought to be due to a decrease in maternal-fetal exchange following a decrease in intervillous space blood flow resulting from uterine contractions. It is seen quite frequently in situations where such complications as toxemia, chronic hypertension, diabetes mellitus, and erythroblastosis fetalis are present. With this pattern, it is thought that the margin of fetal reserve is low and the added stress of repetitive contractions results in fetal compromise.

The lowermost traces, in record C, show an FHR pattern of variable shape where the onset of the deceleration occurs at *variable* times in the contracting phase of the uterus; this has been labeled variable deceleration. This particular FHR pattern is thought to be due to umbilical cord occlusion. It is the most common cause of clinically diagnosed fetal distress on our service and is probably responsible for the majority of caesarean section for this indication. While an FHR pattern of variable deceleration causes a great deal of obstetrical anxiety (FHR frequently drops precipitously from the normal range of 120–160 beats/min to 60 beats/min or less), it can usually be alleviated merely by changing the position of the mother. Thus the uterine contents are redistributed in such a manner that pressure on the umbilical cord is released. In this way the FHR pattern of variable deceleration is markedly modified or completely eliminated, so that caesarean section is averted.

The late-deceleration pattern of FHR. While the FHR pattern of variable deceleration can be recognized to some extent by careful auscultation, the FHR of late deceleration can be easily missed. This is a special problem, since many of

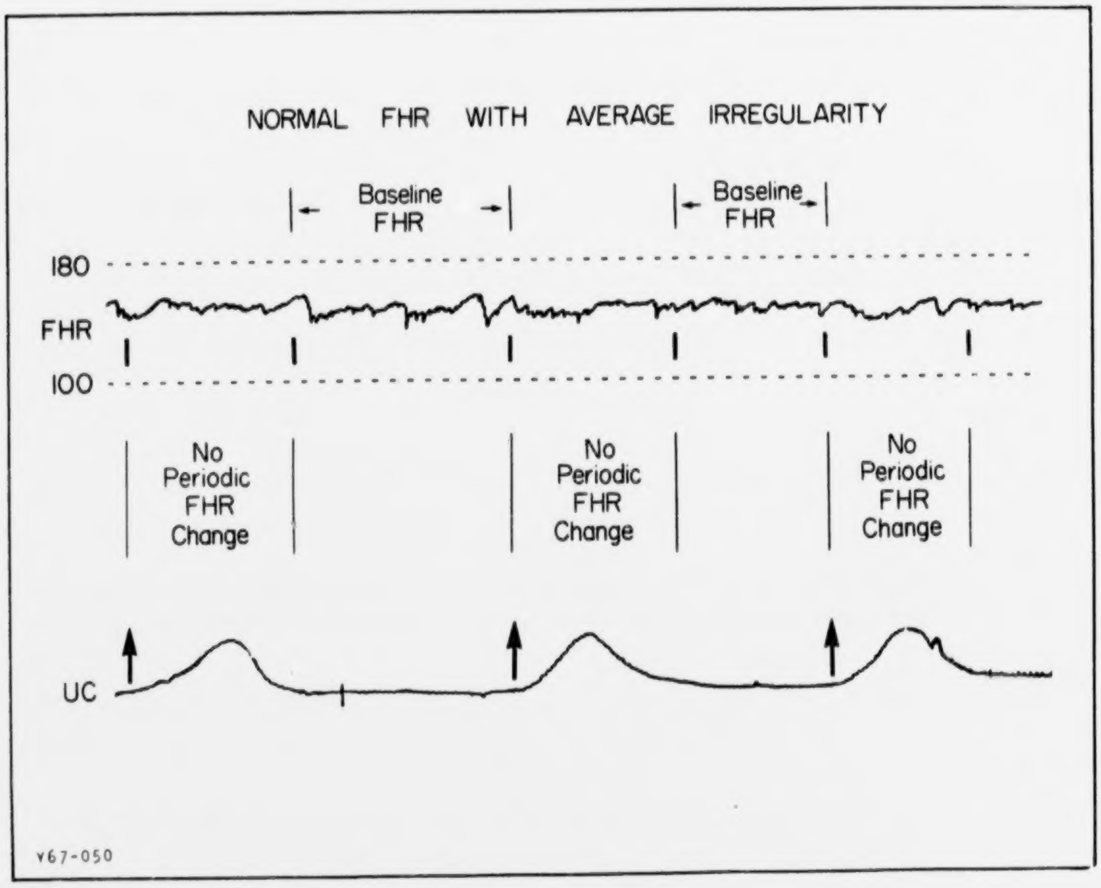


FIGURE 6.—Record showing that periodic accelerations and decelerations of the FHR do not normally occur with all uterine contractions (UC).

the late deceleration patterns are usually found in the normal clinical range. Figure 8 illustrates some of the characteristics of this pattern—a uniform FHR with the onset of the deceleration occurring late in the contracting phase of the uterus. Usually in the range of 120–180 beats/min, the FHR may fall as low as 60 beats-/min. This fall, usually less than 90 seconds long, is associated with fetal acidosis. The late deceleration pattern appears to be directly related to decreased maternal-fetal transfer and may be caused by factors that decrease intervillous space blood flow, that is, uterine hyperactivity, maternal hypotension, and placental dysfunction (fig. 9).

In clinical obstetrical practice, one of the most common causes of this type of FHR pattern is injudicious use of oxytocin or the presence of maternal hypotension, whether this be associated with the maternal supine position or conduction anesthesia. In our studies this particular FHR pattern has been associated with situations in which the fetus has been severely depressed or has died or, in a few instances, in which the infants have later developed neurologic deficits. One of the major difficulties in the management of fetal distress is the absence of clear-cut indices of success or failure. Thus it is difficult to determine the significance of FHR patterns, whether they are innocuous or ominous.

To avoid this difficulty, for the purposes of this discussion, I have chosen as an end point death itself, since this is reasonably sharp delineation. Figure 10 is

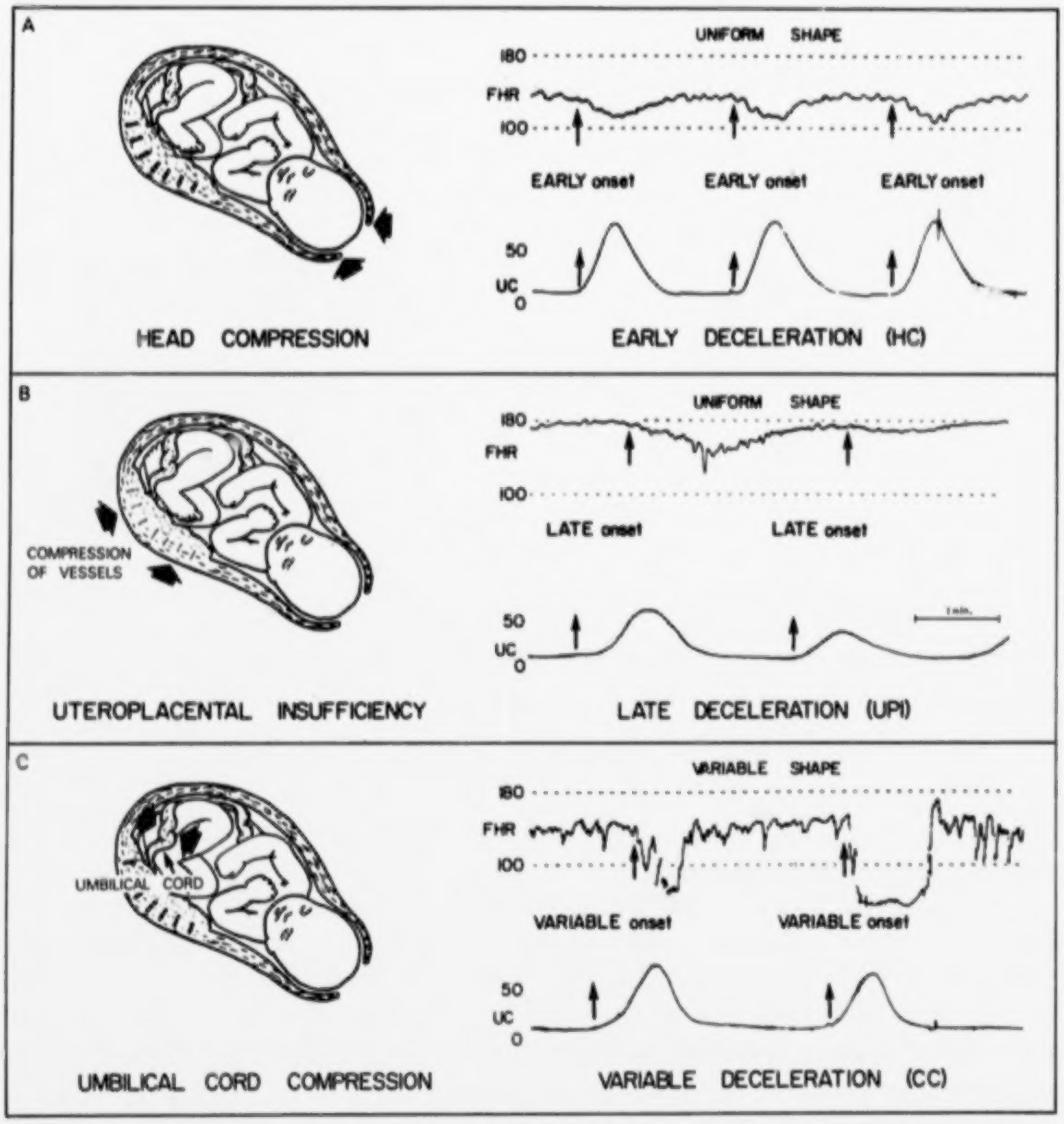

A
UNIFORM SHAPE
180
FHR
100
EARLY onset
EARLY onset
EARLY onset
50
UC
0
HEAD COMPRESSION
EARLY DECELERATION (HC)
B
UNIFORM SHAPE
180
FHR
100
LATE onset
LATE onset
1 min.
50
UC
0
COMPRESSION OF VESSELS
UTEROPLACENTAL INSUFFICIENCY
LATE DECELERATION (UPI)
C
VARIABLE SHAPE
180
FHR
100
VARIABLE onset
VARIABLE onset
50
UC
0
UMBILICAL CORD
UMBILICAL CORD COMPRESSION
VARIABLE DECELERATION (CC)

FIGURE 7.—Deceleration patterns of FHR of consistent clinical correlation.

A: Early deceleration associated with head compression, unassociated with any clinical problems.

B: Late deceleration associated with a decrease in intervillous blood flow seen in toxemia and other maternal-fetal complications.

C: FHR deceleration of variable onset, thought due to compression of the umbilical cord.

the FHR and uterine contraction record of a 28-year-old primigravid patient at 43 weeks of gestation. The contractions (UC) are quite strong and frequent. On the basis of our experience we would say that excessive uterine activity was present. The clinical obstetrician listened to the FHR with a stethoscope between contractions and felt that it was normal. From a clinical standpoint, this was true—until the last few minutes of the lower record. In this instance the FHR did not meet the clinical criteria of fetal distress until a few minutes before fetal death, which took place shortly after the end of this record. This record demonstrates the significance of the late deceleration pattern and the inadequacy of in-

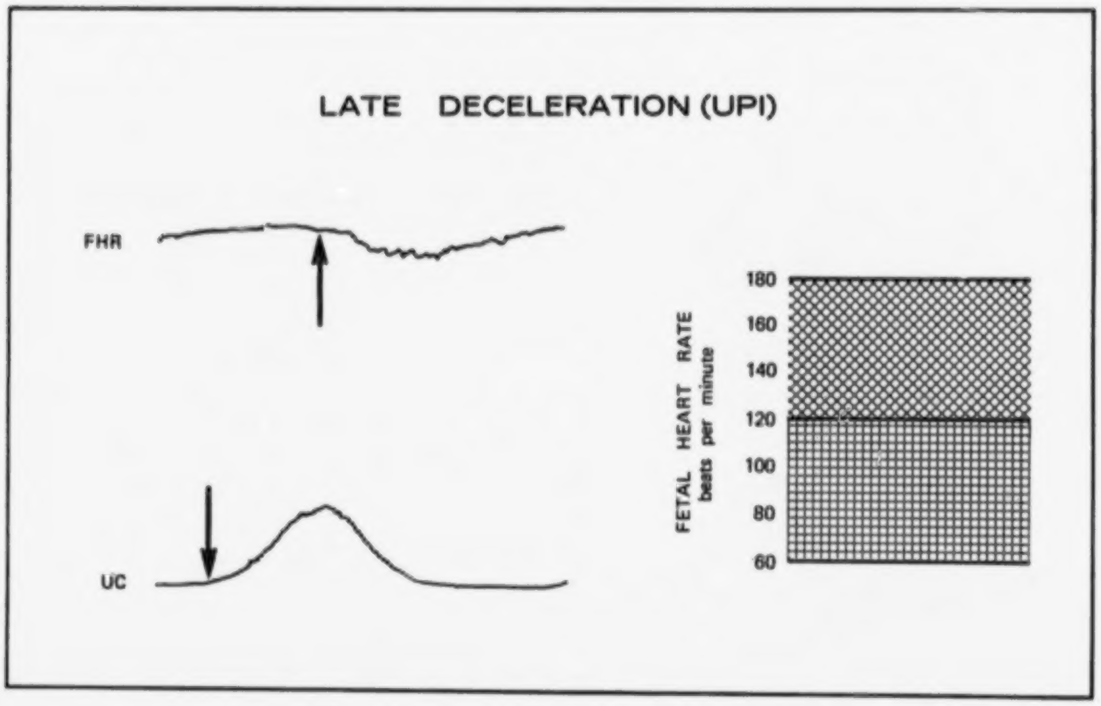


FIGURE 8.—Late deceleration of FHR in which the normal of 120–180 beats/min. may fall as low as 60 beats/min.

termittent auscultatory FHR determination to detect an ominous pattern until a few moments before fetal demise.

Figure 11 is another example of the FHR pattern of late deceleration and demonstrates the use of our present clinical monitoring system. This patient was admitted early in the morning, when the private obstetrician was at home. On initial examination the resident noted the passage of meconium and the very active labor of the patient. He immediately put the patient on the fetal monitoring system and quickly identified the FHR pattern of late deceleration and the marked uterine hyperactivity. He recognized the problem immediately, took the patient to the caesarean section room, changed the maternal position, and administered high concentrations of oxygen to the mother. As can be seen from the record, there was some modification of the FHR pattern after these measures were instituted. Just before the start of the caesarean section, the patient was examined and found to be fully dilated. Delivery was readily accomplished with an easy forceps delivery. Unfortunately, the baby did not breathe and died in the first few minutes of life. If this FHR in this record had been determined in the intervals between contractions with a stethoscope, it would have been in the normal range.

Figure 12, another record of the late deceleration pattern, was made in 1957 when contractions were not recorded with an intrauterine catheter but by abdominal palpation. The duration of the contractions is indicated by cross-hatched oblongs. The FHR deceleration was late in the contracting phase of the uterus. In this patient, it persisted for about six hours. The FHR determined in the intervals between contractions, after waiting 30 seconds until they were over, is seen to have a normal level most of the time. The child from whom this record

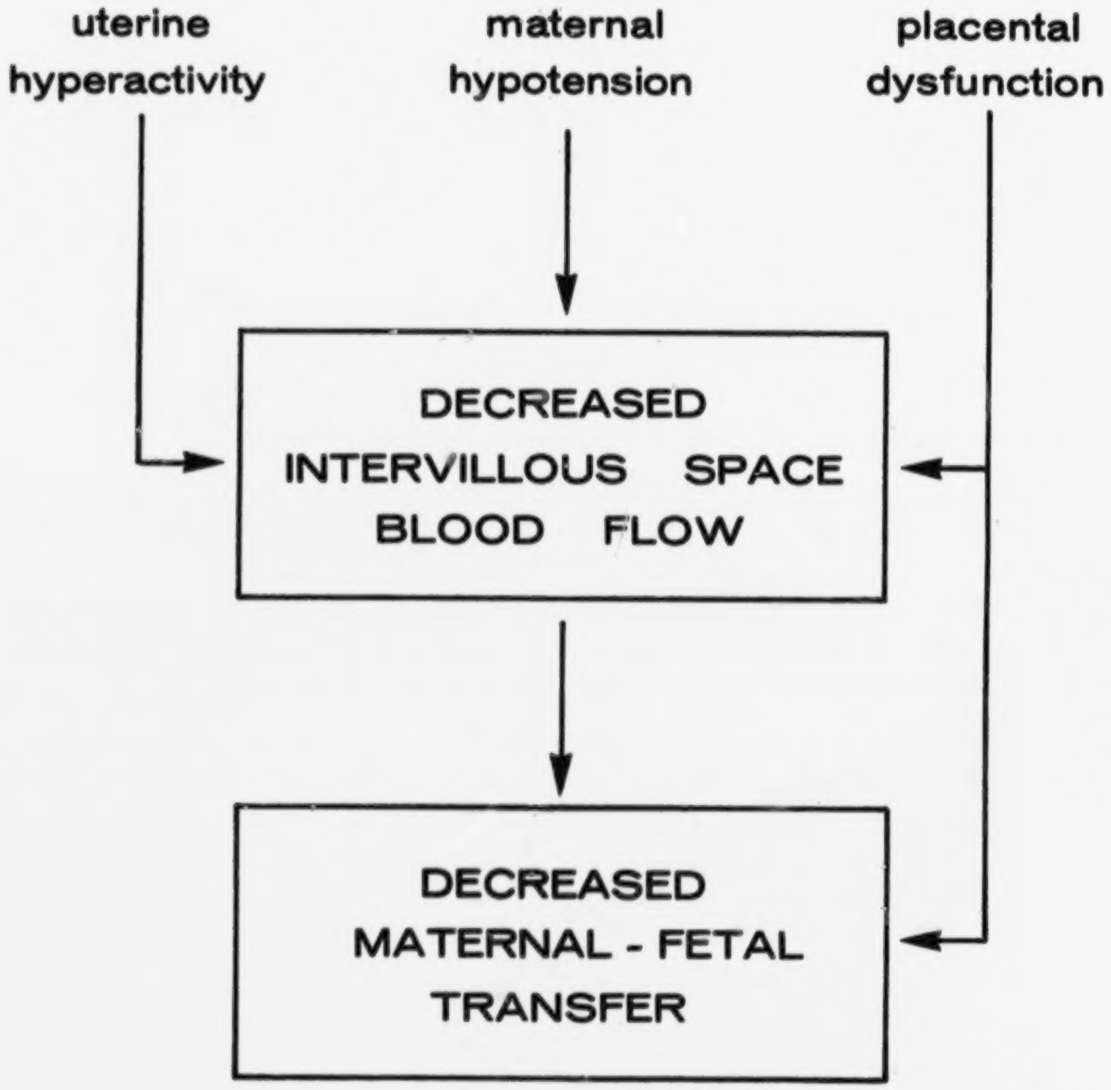

uterine hyperactivity
maternal hypotension
placental dysfunction
DECREASED INTERVILLOUS SPACE BLOOD FLOW
DECREASED MATERNAL - FETAL TRANSFER

FIGURE 9.—Pathogenesis of decreased maternal-fetal transfer characterized by late deceleration pattern.

was made is now 11 years old and has shown severe mental retardation since two years of age. Again, here is an FHR level that does not meet our present clinical criteria of fetal distress, yet appears to be quite ominous.

As far as can be determined, the FHR pattern of late deceleration is ominous and, in our studies, frequently has been associated with fetal death and damage. It is important, therefore, for us to recognize that an FHR pattern in the presently accepted clinical normal range may be quite ominous.

As an aside, I would like to discuss the irregularity of the FHR, since it appears that momentary variations in the interval between successive heart beats are important, reflecting as they do the integrity of the nervous mechanisms controlling the heart. The graphs of fig. 13 were made from FECG data. The vertical axis shows the interval difference between successive FECG peaks. The scale is ±40 milliseconds. The horizontal axis shows time in seconds. The graphs have been constructed by considering the intervals t_1, t_2, t_3, . . . t_n, where t is the

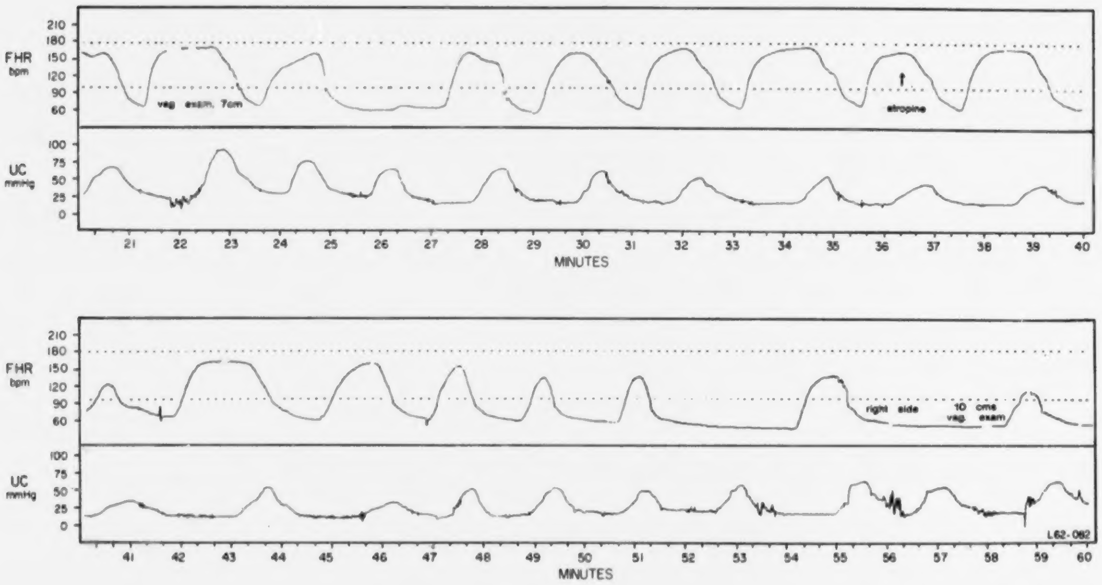


Figure 10.—FHR and hyperactive uterine contractions, 28-year-old primagravida at 43 weeks gestation. No auscultatory change in FHR was noted until a few minutes before fetal death, shortly after end of this record.

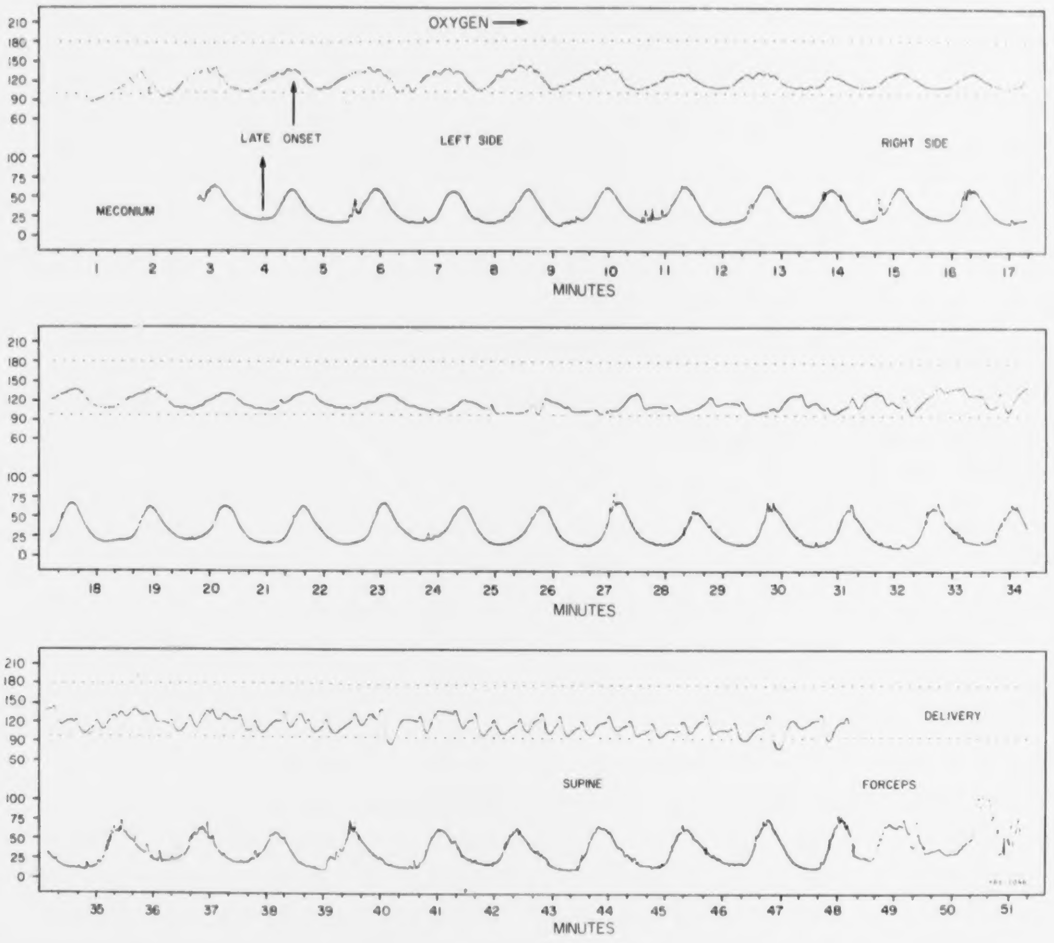


Figure 11.—Hyperactive contractions and deceleration FHR sufficiently modified by oxygen and change in position to allow forceps delivery.

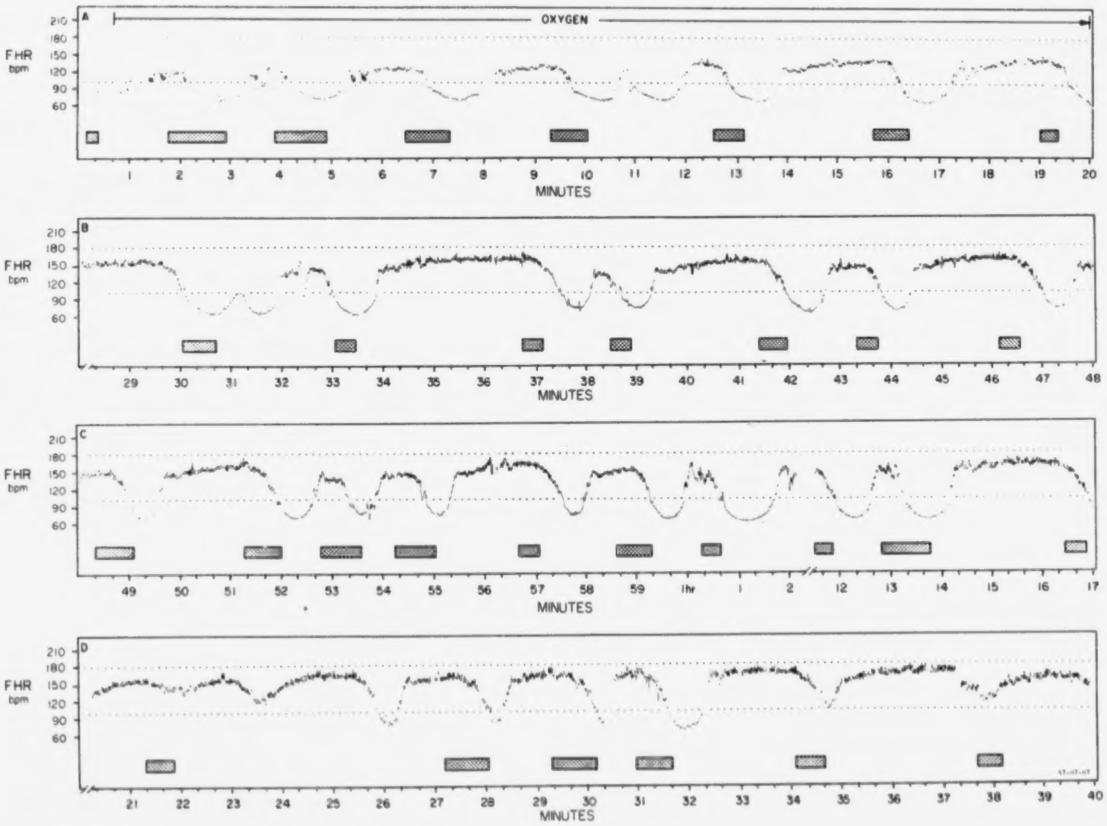


FIGURE 12.—Late deceleration of FHR as determined by abdominal palpation of uterine contractions (cross-hatched). Child severely retarded at age 11 years.

interval between successive FECG's and by calculating the interval difference between successive fetal heart beats. This difference is displayed as vertical excursions. Figure 13a shows the variation in interval difference before maternal nembutal administration; fig. 13b, the decrease in interval difference after nembutal administration. FHR becomes relatively fixed after the administration of this drug. Similar decreases in interval differences between successive fetal heart beats are also seen in fetal immaturity (13c) and just before fetal death (13d–13f).

DISCUSSION

DOCTOR DESMOND: In relation to the last point which Dr. Hon presented, I would like to present some more information which confirms these observations. For example, with anencephaly, some of the records show a very stable, smooth tracing with very little difference between the intervals of successive beats. It seems that in these cases a large part of the central nervous system is lacking.

Other situations in which we have found a very smooth tracing, with very little change in the intervals, are cases of fetal distress where the fetus has suffered for a long time; for example, cases of severe toxemia where the fetus died shortly after birth. I fully agree with Dr. Hon that the absence of FHR irregularities is a very bad sign. It either indicates depression of the central nervous system, damage of the central nervous system from chronic asphyxia, or lack of certain parts of the central nervous system.

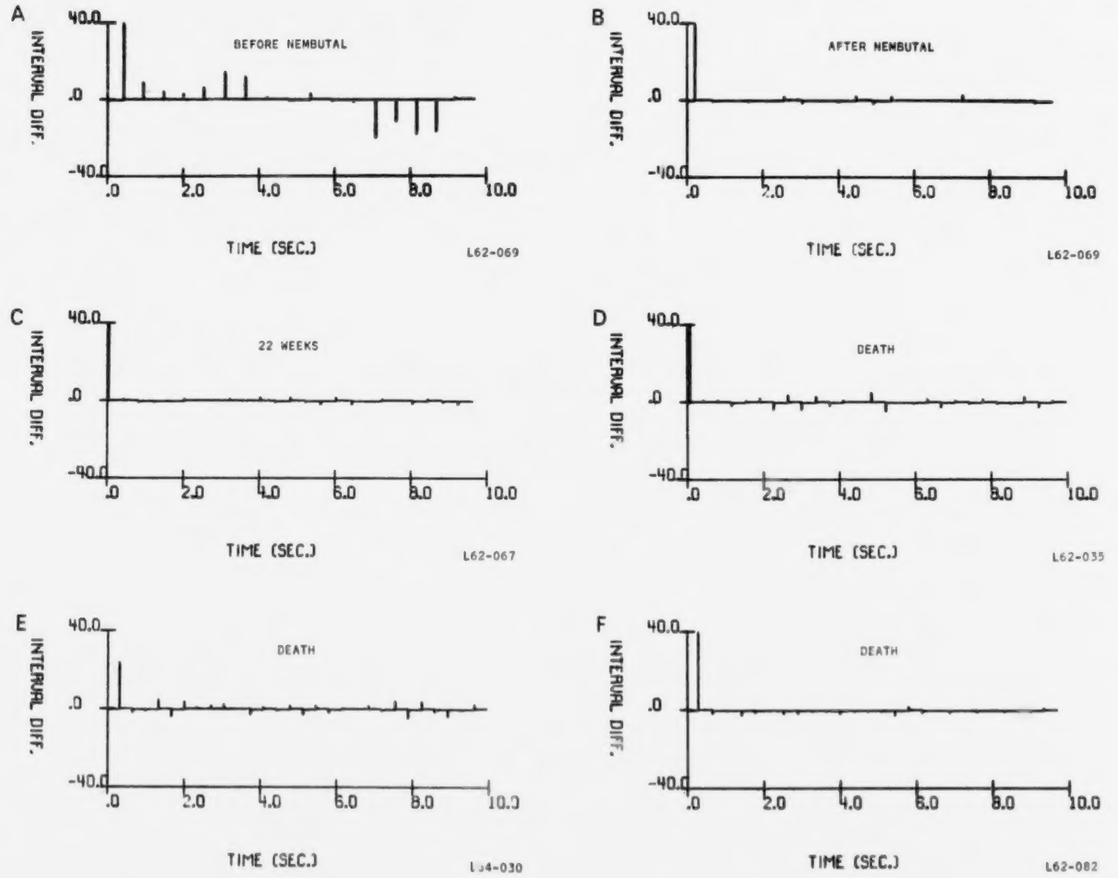


FIGURE 13.—Interval difference of successive peaks of the FECG. A and B: Effect of nembutal. Decrease in interval differences is also seen in fetal immaturity (c) and just prior to fetal death (D,E,F).

DOCTOR ADAMS: Is there any circulation to the brain if the fetal head is severely compressed, and is this slowing of pulse a corroborative factor related to a vagal influence?

DOCTOR HON: Well, it can be. It depends on what causes the slowing. If one looks at the patterns of cord compression, which have been best studied, various mechanisms appear to be operating. If one compresses the umbilical vein alone, one produces the deceleration of heart rate and hypotension is present. If the umbilical arteries alone are compressed, there is still a deceleration in heart rate. In this case, however, hypertension is present. If both vein and artery are compressed together, you still get a drop in heart rate but you may have normotension. These studies were done at the time of elective caesarean section. A loop of cord was pulled up through a window in the uterus and a catheter was placed in the umbilical artery. Short-lived umbilical vessel compression studies were then done. These human studies confirmed the original hypothesis which was based on the work of Barcroft in the fetal lamb. The basis of present concepts of FHR patterns, as we have presented them, is well founded in comparative physiology. When we say, this is the FHR pattern of cord compression, the statement is supported by the animal work and by direct short-term human studies in intact fetuses. It has been repeated in small fetuses where the umbilical cord had prolapsed, so I think this is very well documented as a distinct FHR pattern.

Doctor Adams: Well, the plain fact is that you don't know what the cerebral circulation is with a slowing of the pulse.

Doctor Hon: No, we don't.

Doctor Barlow: It seems to me you're asking Dr. Hon questions that we should be asking his experimental neurologist. One thing I would like to ask Dr. Hon, though, because it seems an important base to further studies of cerebral blood flow during this phenomenon, is the state of the fetus' blood pressure. The blood flow is very much related to blood pressure, expecially when there is hypercapnia, at least as far as we know from studies on the mature system. All of these systemic factors are of critical importance as a next step before one goes on to study more directly the actual fluctuations of blood flow during these events that you've described. I think this is a point of critical importance. As far as I know, the information just is not available. However, the technology for obtaining it in the experimental animal is available.

Doctor Hon: We have a preparation, indeed, in which we can study this. Doctor Quilligan has a preparation which uses a fetal lamb approximately at term. The fetal head is delivered at caesarean section and catheters are placed in the carotid arteries and the jugular vein. EEG and ECG electrodes are attached to both the fetus and mother. The fetus is put back in the uterus, then we wait until the system stabilizes before beginning our studies.

Doctor Jacobson: I would wonder whether Dr. Caldeyro-Barcia and Dr. Hon have any plans to make a mechanical model of the effects of cerebral blood flow. It would seem to me, from their very fine and sophisticated data, that it would be possible to make an artificial uterus with appropriate sensors and pumps, make a simulated head, control flows through it with appropriate transfusors and pumps, and get some idea of the effect of changes in uterine pressure, both as the function of pressure and the function of time. Rather than working from the experimental animal preparation, which is quite complex, it might be better to go to the simplest situation and work back.

Doctor Hon: Well, yes. I have thought a great deal about physiologic control systems. We have a small analog computer but I don't think I have enough information to even begin the study. Maybe when we've done more animal studies we can get a better look at it. We have looked at the nervous mechanisms controlling the heart by looking at the beat-to-beat differences. One can set up a very simple servomechanism. When one dampens the sensitivity of the servomechanism, the changes that we see in the FHR can be duplicated easily. However, all this is rather at the periphery of the problem.

Participant: This data and that of Dr. Caldeyro-Barcia's would indicate to me that there are certain times when there is no perfusion of the brain. Certainly when you have a 50-millimeter intrauterine pressure and the blood pressure on the top of the fetal head is zero, it would be very difficult to perfuse through capillaries, arterioles, and venules. How long does this have to be maintained? What is the area under the curve at which the damage is produced?

Doctor Hon: Doctor George Misrahy placed polarographic electrodes in the fetal guinea pig's brain and did head compression studies and observed transitory sharp drops in oxygen tension. From a clinical standpoint, after reviewing literally thousands of head compression patterns, we can't find anything pathological either in the pH studies, in electrocardiograms, or in the infant followup. The infant followups aren't all they ought to be, however. Since these FHR patterns occur frequently, if they were bad you would expect them to show up clinically.

Doctor Alvord: Doctor Caldeyro-Barcia, did you have a comment about this?

Doctor Caldeyro-Barcia: Yes, about the changes in fetal blood flow in this condition. There have been fairly complete studies in animals. In humans, the studies have been more restricted. However, it seems likely that when a fetus is in moderate hypoxia, as Dr. Hon stated, the blood pressure is high. In this condition you have a vasoconstriction including the skin, the muscles, the splanchnic area, the kidneys, and the lungs. The blood flow is minimal through all these areas. There is increased blood flow through the brain and the coronary arteries. This seems to be a defensive mechanism. It has been shown in several species and in the human that this is the situation. This is the position when the fetus is successfully defending itself in the first stages. When the fetus starts to fail, the arterial pressure lowers and the blood flow to the brain is diminished. This is when the damage starts.

Doctor Drorbaugh: Well, I think that it will be a long time before we're able to blend clinical information of the kind we're getting with the physiologic data of Dr. Hon and Dr. Caldeyro-Barcia. The comment I wanted to make is that the studies of the blood pressure in asphyxiated newborns would support the idea of Dr. Caldeyro-Barcia. Under stress, the newborn has a transient rise in arterial pressure followed by a dip. This could be mediated by vasoconstriction so that at the time of stress, with a fall in FHR, there might indeed be a rise in arterial pressure. Just one other comment. From a pediatrician's point of view, there is quite a bit of data on blood pressure and cardiac output and of circulatory resistance in the newborn which could form a base for similar kinds of measurements, if they could be made, in the fetus.

Doctor Hon: We have, indeed, studied newborns. They must number at least 200. Where we have blood pressures in the first hour of life, what you say is true. In the newborn, if the baby is quite depressed, the blood-pressure is quite low and the pH's are quite low. However, it is difficult to extrapolate from this baby back to the fetus. What goes on in the uterus may be entirely different.

Doctor Bering: Well, I was going to ask a question in the context of what we're discussing. It seems to me that, if I've gotten the message, the trauma of labor, in the general case, exerts its effect in damaging the brain not by physical trauma *per se,* but secondarily, by producing anoxia as a result of physiologic effects on the fetal circulation. Is this your feeling?

Doctor Hon: Yes, that is absolutely right, Dr. Bering. My experience with physical trauma, such as difficult mid-forceps, is practically nil. Obstetrics has moved away from that kind of trauma. I think we have to look upon the contraction as a stress, a repetitive stress to the fetus. With long labor we give the fetus a much higher level of stress than we do in a short labor. We are trying to teach obstetricians that labor is a repetitive stress and that it can be detrimental to the fetus; one must carefully watch the frequency and amplitude of contractions; and maternal blood pressure must be maintained.

166 581

REFERENCES

Caldeyro-Barcia, R., et al.: Effects of abnormal uterine contractions on a human fetus. *Mod. Probl. Pediat. 8: 267–295, 1963.*

Caldeyro-Barcia, R., et al.: "Control of human fetal heart rate during labor," in *International Symposium on the Heart and Circulation in the Newborn and Infant,* (ed.) Donald E. Cassels, New York: Grune & Stratton, 1966, pp 7–36.

Desmond, M. M., Rudolph, A. J., and Phitaksphraiwan, P.: The transitional care nursery. A mechanism for preventive medicine in the newborn. *Pediat. Clin. N. Amer., 13: 651–668, (Aug) 1966.*

Greiss, F. C., Jr.: Effect of labor on uterine blood flow; Observations on gravid ewes. *Amer. J. Obstet. Gynec., 93: 917–923 (Dec) 1965.*

Greiss, F. C., Jr., and Anderson, S. G.: Uterine blood flow during labor. *Clin. Obstet. Gynec. 11: 96–109, (Mar) 1968.*

Hon, E. H.: The electronic evaluation of the fetal heart rate. Preliminary report. *Amer. J. Obstet. Gynec., 75: 1215–1230, (June) 1958.*

Hon, E. H.: Observations on "pathologic" fetal bradycardia. *Amer. J. Obstet. Gynec., 77: 1084–1099, (May) 1959.*

Hon, E. H.: The instrumentation of fetal heart rate and fetal electrocardiography. I. A fetal heart monitor. *Conn. Med., 24: 289–293, (May) 1960.*

Hon, E. H.: The classification of fetal heart rate. I. A working classification. *Obstet. Gynec. 22: 137–146, (Aug) 1963.*

Hon, E. H.: Instrumentation of fetal heart rate and fetal electrocardiography. II. A vaginal electrode. *Amer. J. Obstet. Gynec., 86: 772–784, (July 15) 1963.*

Hon, E. H.: The detection of fetal distress. *Fifth World Congress of Gynaecology and Obstetrics,* (ed.) Carl Wood, Australia: Butterworth & Co., 1967, p 58.

Hon, E. H., and Lee, S. T.: Electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death, further observations. *Amer. J. Obstet. Gynec., 87: 814–826, (Nov 15) 1963.*

Hon, E. H., and Quilligan, E. J.: The classification of fetal heart rate. II. A revised working classification. *Conn. Med., 31: 779–784, (Nov) 1967.*

Lee, S. T., and Hon, E. H.: Fetal hemodynamic response to umbilical cord compression. *Obstet. Gynec., 22: 553–562, (Nov) 1963.*

Martin, C. B., Jr., et al.: Intermittant functioning of the uteroplacental arteries. *Amer. J. Obstet. Gynec. 90: 819–823, (Nov 15) 1964.*

Quilligan, E. J., Katigbak, E., and Hofschild, J.: Correlation of fetal heart rate patterns and blood gas values. II. Bradycardia. *Amer. J. Obstet. Gynec., 91: 1123–1132, (April 15) 1965.*

Ramsey, E. M., Martin, C. B., Jr., and Donner, M. W.: Fetal and maternal placental circulations. Simultaneous visualization in monkeys by radiography. *Amer. J. Obstet. Gynec., 98: 419–423 (June 1) 1967.*

Rudolph, A. J., Vallbona, C., and Desmond, M. M.: Cardiodynamic studies in the newborn. III. Heart rate patterns in infants with idiopathic respiratory distress syndrome. *Pediatrics, 36: 551–559 (Oct) 1965.*

Vallbona, C., et al.: Patterns of sinus arrhythmia in patients with lesions of the central nervous system. *Am. J .Cardiol., 16: 379–389, (Sept) 1965.*

TRAUMA TO NECK VESSELS LEADING TO CEREBRAL DAMAGE

Peter O. Yates, M.D., M.C. Path.
Department of Pathology
The University of Manchester
Manchester, England

One of the main difficulties facing pathologists in the interpretation of sequential events is that they are usually able to examine the situation at only one point in time. In a study of the effects of birth trauma to the brain this is a particularly serious difficulty. Where death occurs in the neonatal period, we may look at the situation in the brain and the arteries supplying the brain, find acute lesions, and attempt to interpret what might have happened had the child survived.

At the other end of the scale, in examining the brain from a patient showing mental retardation or cerebral palsy in late childhood or even adult life, one attempts retrospectively to guess at what might have been the original lesion. Cause and effect are often separated by a long period of time. This process is, of course, very much easier in the mature brain, where we have been quite clear for more than a hundred years that certain lesions are due to occlusion of the arteries supplying the brain. This is because the lesions of the brain itself are uncomplicated by later developmental changes. If, for example, the middle cerebral artery or vertebral artery of an adult is obstructed, then the pathological changes which follow are fairly clear-cut—infarction, removal of debris, and scarring.

In the child, the situation is quite different. Here we may have infarction of a territory which has little or no function at the time of birth, so that neurological disability may become obvious only later in life; furthermore, the absence of such a damaged area will have secondary effects on territories that depended upon it for their own correct maturation. So, pathologically, the lesions we may find in the birth-damaged brain of a child dying perhaps at the age of 6 or 7 may owe more to maldevelopment than to the original arterial ischemia.

However, although the result may look quite unlike that which we all agree to be an infarct in the mature organ, the pattern of location of the damage may give a strong indication that the lesions produced at the time of birth have an arterial cause.

Whether the baby is a breech or a head presentation, the part often stretched and twisted during delivery is the neck. The most obvious result will be damage to the spinal cord. One aspect of damage to the spine is that the vertebral arteries are intimately related to the cervical vertebrae and may themselves be involved in the damage. If this should occur, then it would be particularly significant and apparent at the time of birth, since it is at this period that the vegetative functions of the brain stem are established.

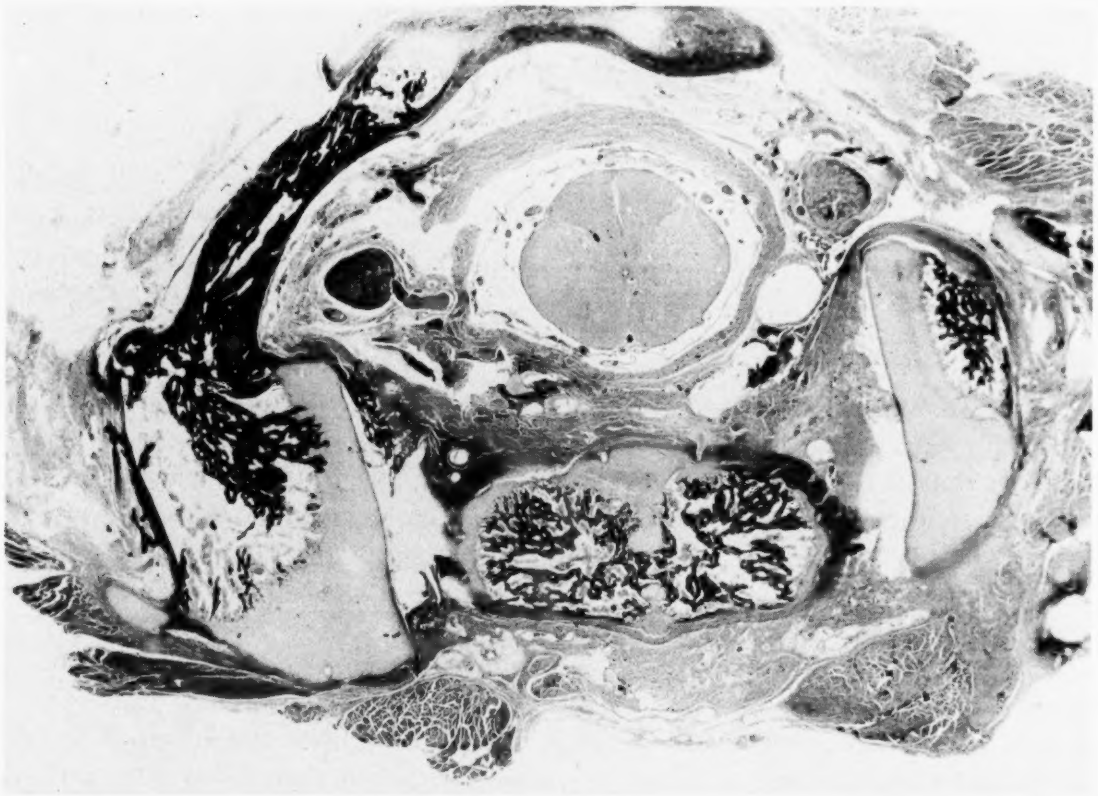


FIGURE 1.—Transverse section of cervical spine showing tearing of dura around cord.

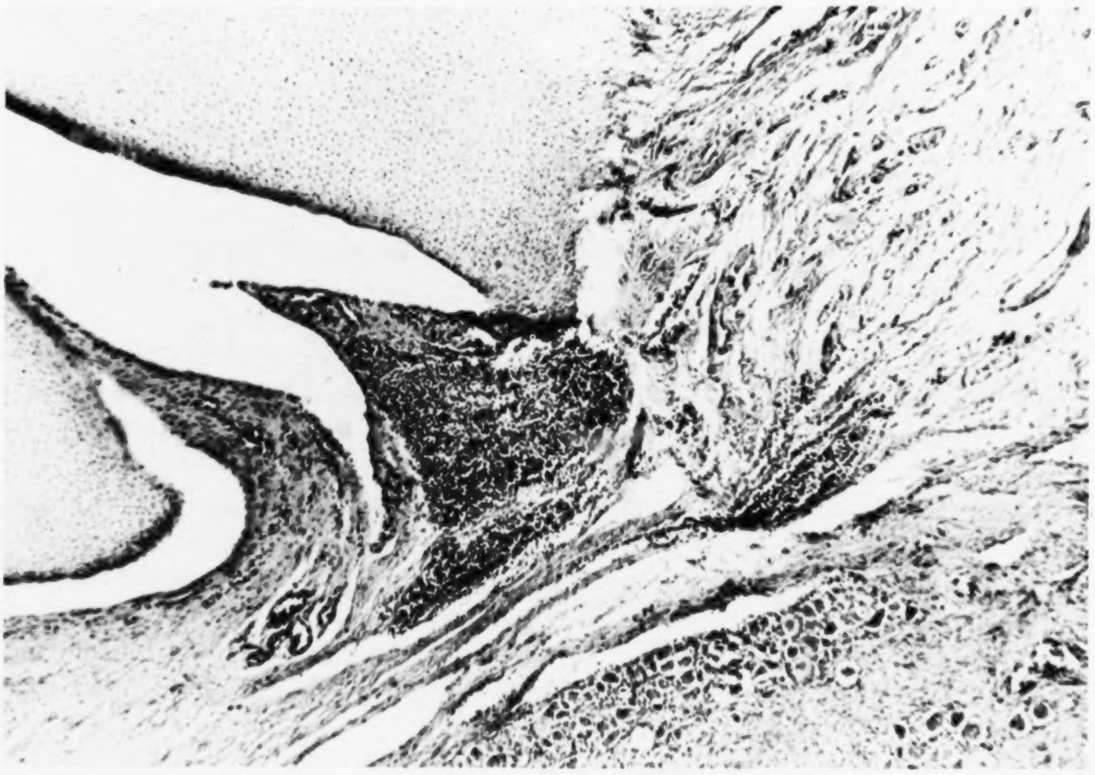


FIGURE 2.—Torn joint capsule with haemorrhage.

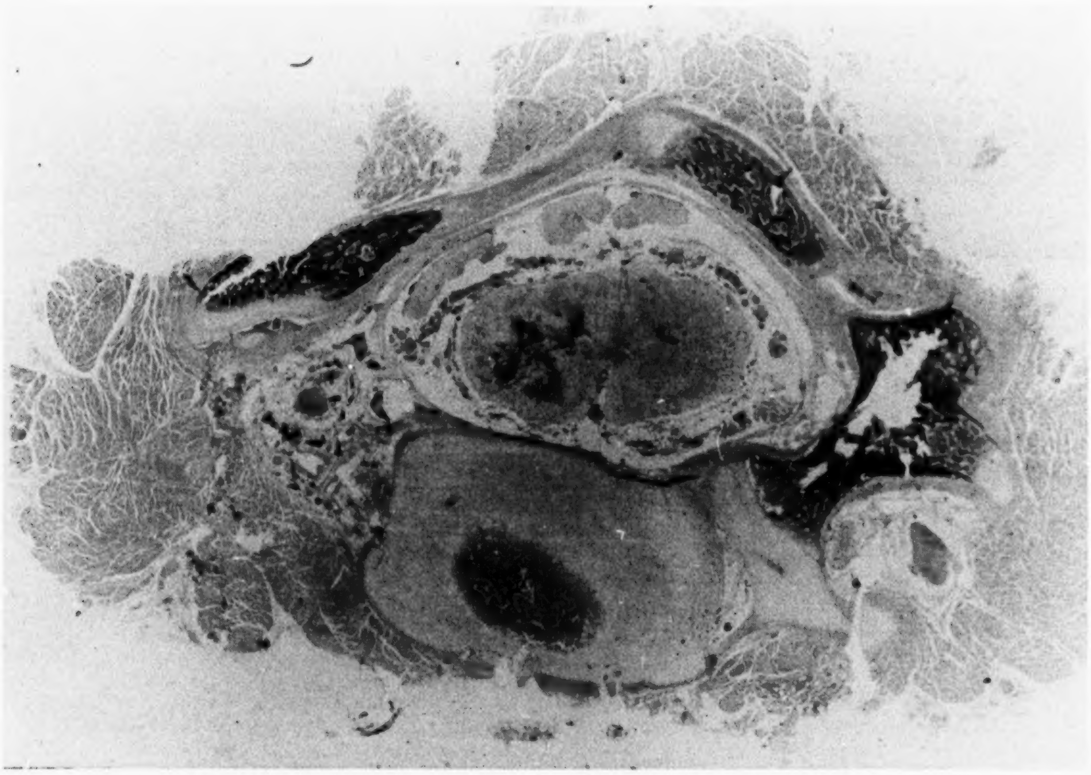


FIGURE 3.—Contusion of spinal cord.

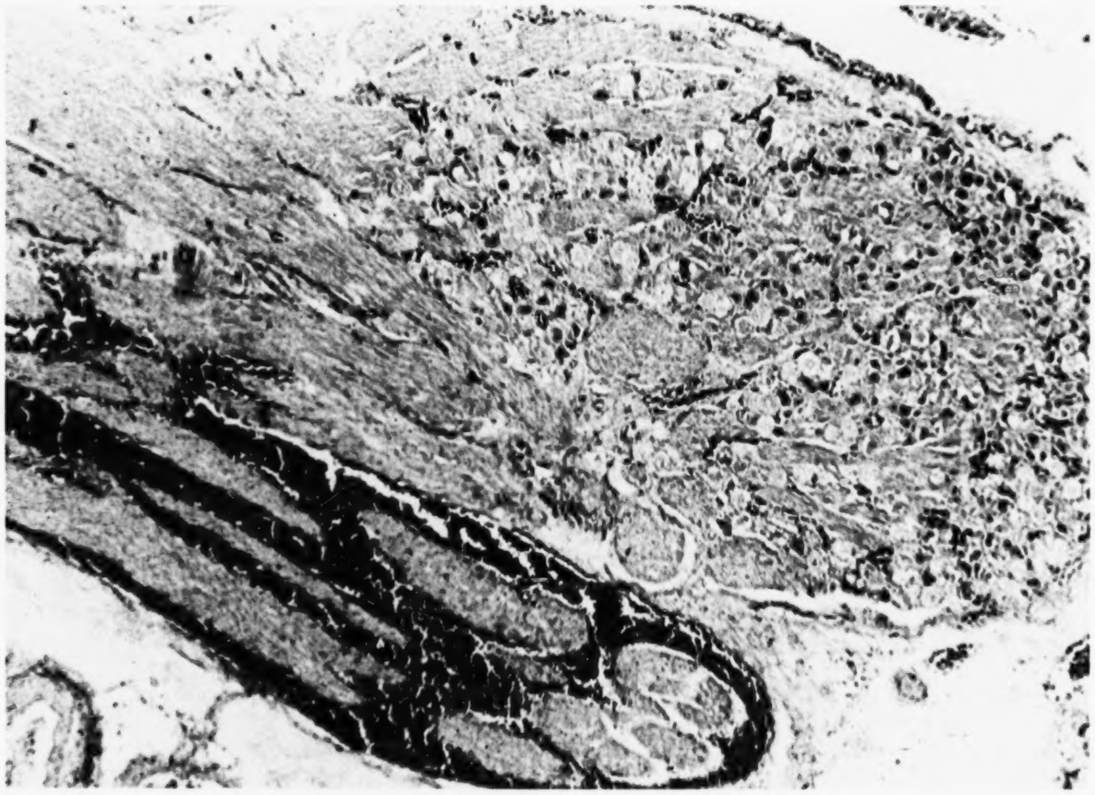


FIGURE 4.—Torn anterior spinal nerve root.

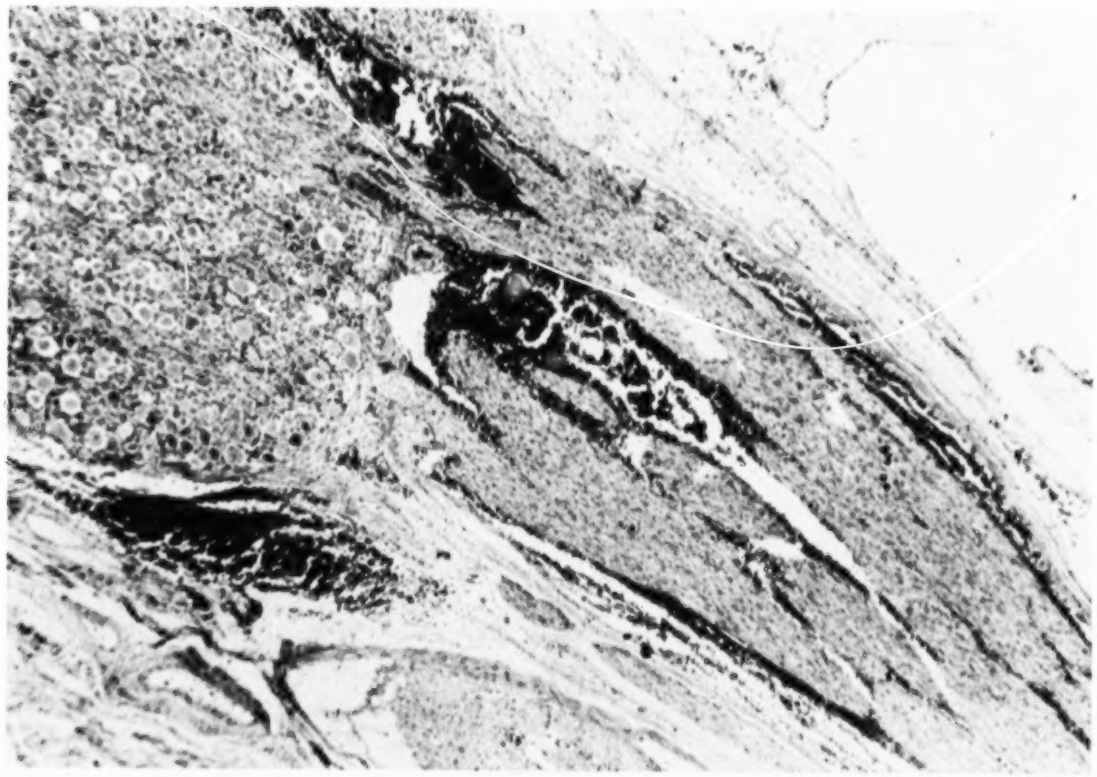


FIGURE 5.—Posterior nerve root partially torn away from the ganglion.

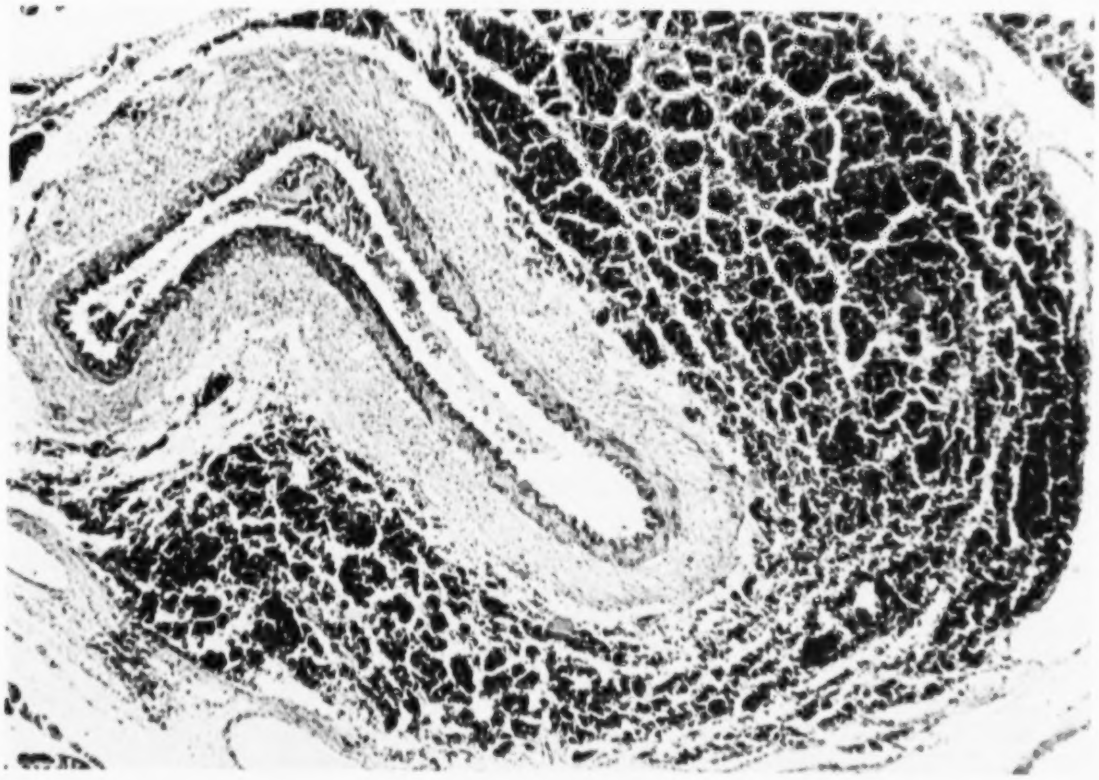


FIGURE 6.—Compression of vertebral artery by adventitial haematoma.

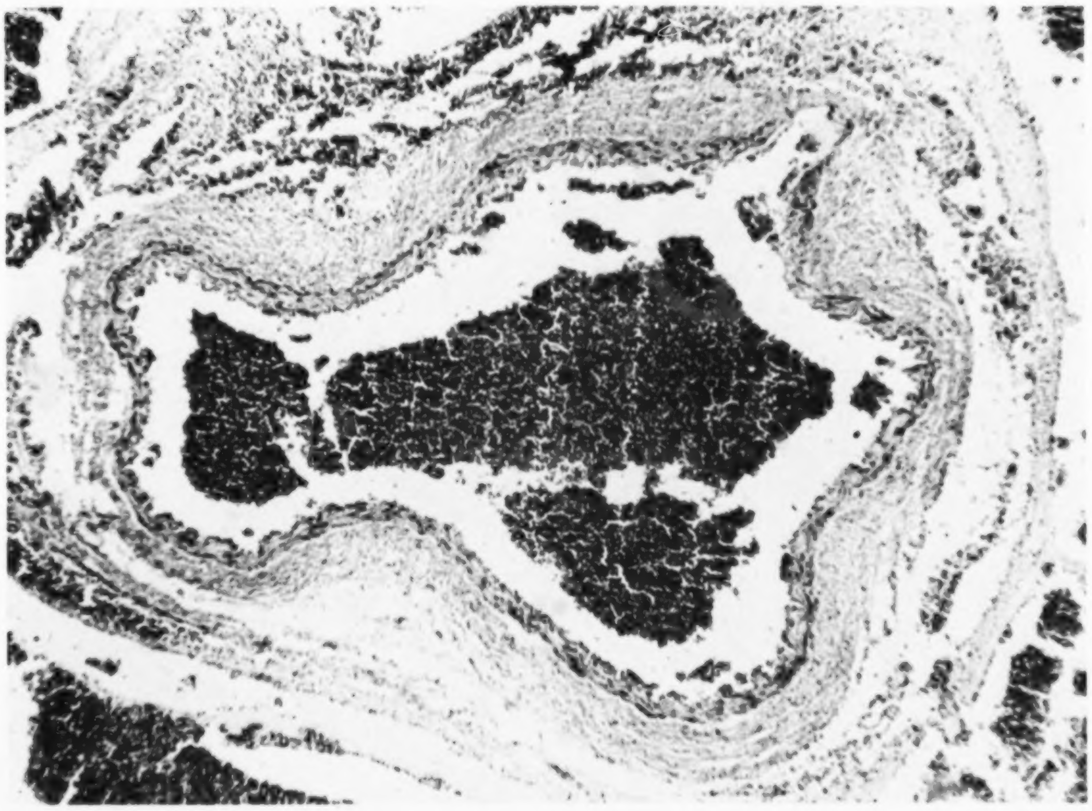


FIGURE 7.—Vertebral artery showing dissection of advential coat in the region of a small arterial twig.

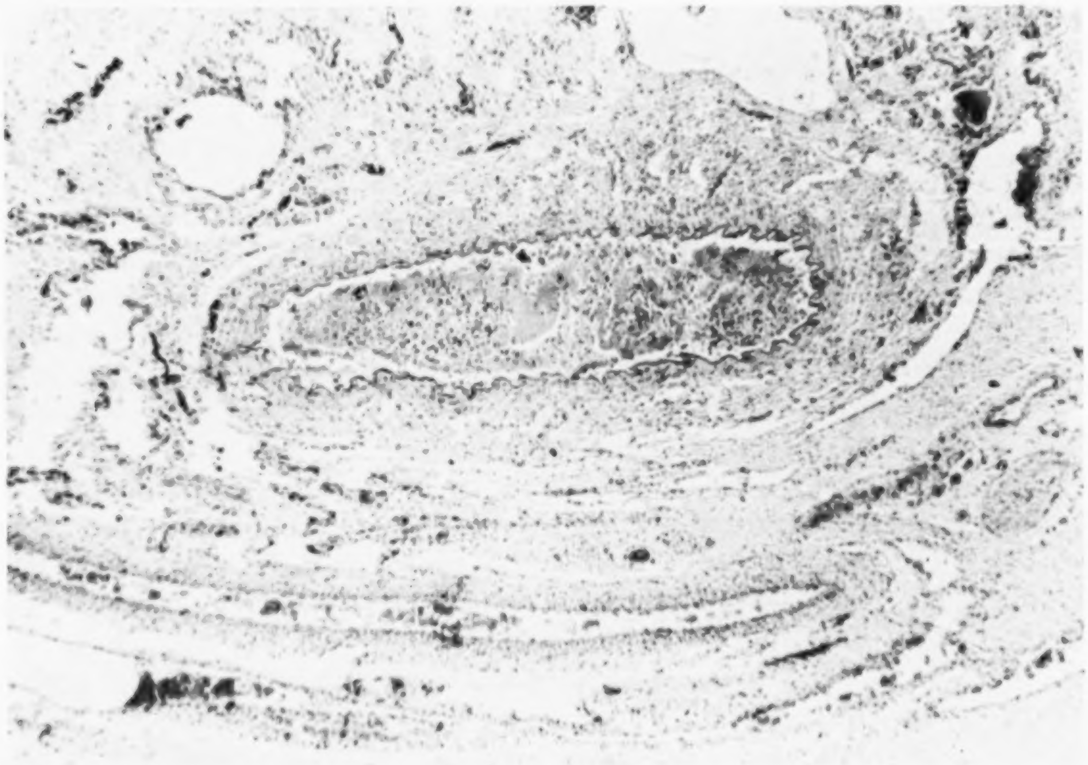


FIGURE 8.—Thrombus in vertebral artery at region of C.2, probably embolic.

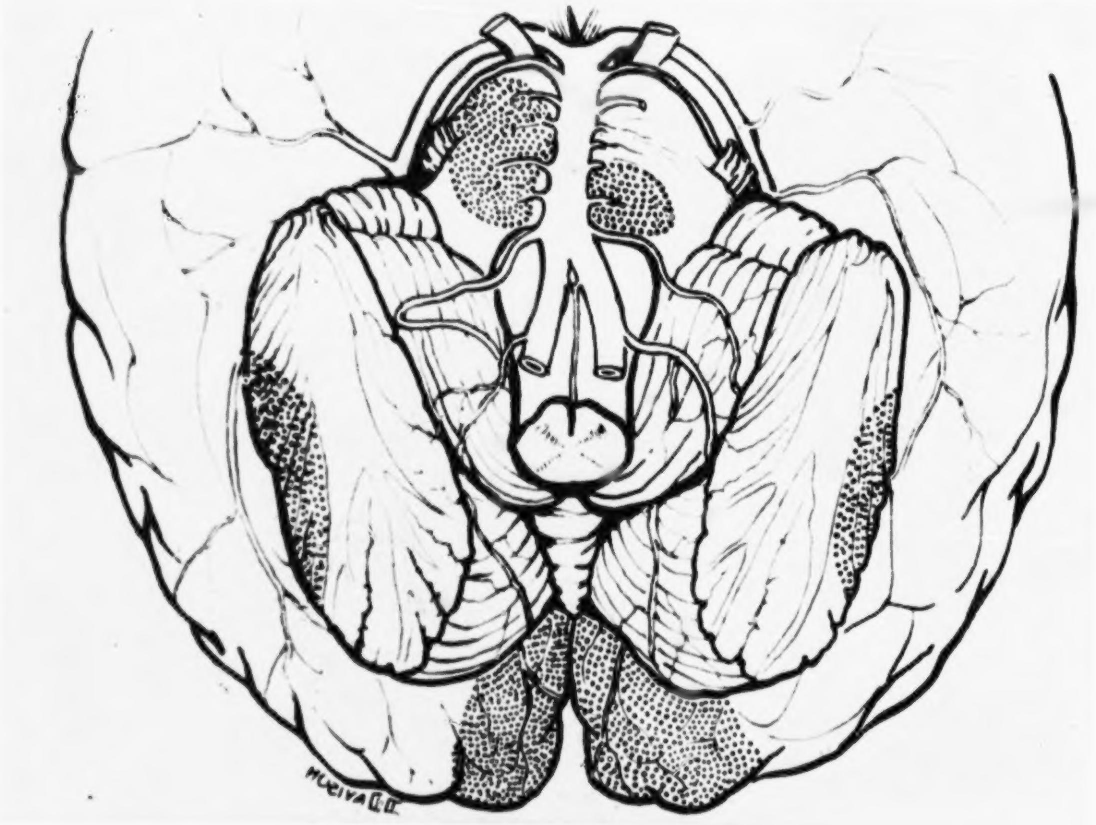


FIGURE 9.—Typical distribution of lesions of the brain as found in an adult case of obstructive vertebral arteries, indicating the pattern of damage to be expected in infants.

The effects of such ischemia may be evident as cardiorespiratory failure or disturbance of temperature control; later there might appear the results of cranial nerve palsy, e.g., squints, damage to the audiovestibular nuclei of the brain stem, damage to the inner ear, interference with the reticular tissues of the upper brain stem which may show as hyperkinetic states.

I investigated the state of the vertebral artery and other structures in the cervical spine of 250 cases of death in the perinatal period. These were a sample from 1,100 stillborn and neonatal deaths that occurred out of 14,000 births in a hospital where there are perhaps a greater number of abnormal births than one would expect in the general population.

I excluded from the sample fetuses with such conditions as hydrocephalus, anencephalus, and a severe degree of maceration indicating that they had been dead for a considerable time in utero before birth. With these exceptions, the choice of cases was random. The cervical vertebrae were removed and examined throughout their length by histological methods.

General trauma to the cervical spine was present in over a quarter of the cases; direct damage to the spinal cord was not common and only really found in breech delivery (only 1.6 percent; figs. 1–3); the spinal nerve roots were frequently found to be torn (10 percent; figs. 4–5); one or both vertebral arteries were damaged (17 percent). The type of lesion found most in these arteries was hemorrhage into the adventitial coat, splitting the coat or apparently compressing the artery to a varying degree (figs. 6–8). The hemorrhage extended about 1 cm up the wall of the artery and usually resulted from the tearing of one of the branches of the vertebral artery at their junction with the major trunk. The main vessels themselves were never torn. Although a pathologist can say very little about arterial vasospasm, it seems quite clear that this may occur because of such lesions in the vessel wall.

There is considerable evidence to suggest that a stenosis or occlusion of the vertebral arteries at the time of birth, even for a short period of time, and even by a lesion that might later be reabsorbed, is an important factor in the production of cerebral palsy. The distribution of the lesions found in a number of cases of cerebral palsy and a comparison with what we find in undoubted vertebral arterial lesions in adults, bear this out (fig. 9). For example, Norman in 1953 found that five out of 35 cases of cerebral palsy had been characterized from a neurologic point of view by cortical blindness, and bilateral calcarine gyral damage was found pathologically. Many people have reported similar lesions of the calcarine cortex. There is a further subgroup of cerebral palsy known as the atactic cerebellar type, the only adequate explanation for which must be, to my mind, an ischemic lesion at the time of birth, the result of some sort of obstruction of the vertebral arteries.

Lastly I wish to point out that the scarring of the temporal lobe, found in many cases of temporal lobe epilepsy, occurs in territory supplied by the vertebral arteries.

DISCUSSION

Doctor Towbin: I submit that the damage here is direct, not indirect by way of occlusion of the arteries. I think that when one looks at the amount of damaged organic material present in the brain stem and in the cord, one cannot come away without thinking that this is an adult who had a dramatic, smashing, tearing lesion of the cord.

One doesn't have to look for indirect mechanisms. This is a really direct trauma on the upper cord, the brain stem. Doctor Yates, you said that you didn't look at the little ones, and I didn't either until a while ago. But very importantly a few weeks ago, I did a 300 gram fetus that had a massive upper cervical cord damage, the same data that you showed here. It has nothing to do with the obstetricians, if this is any comfort. This is patently the result of the descent of this fragile fetus down an unrelaxed and rigid birth canal, through a rigid cervix, in which the fetus gets it in the neck.

Doctor Yates: Direct damage? Yes, I would accept direct damage to the spinal cord. I would find it difficult to accept direct damage to the brain stem, particularly the upper brain stem, but obviously direct damage does have a contribution to make here. I'd also point out that the lesions that I described are mostly unilateral. Now this would suggest to me some close relationship to direct responsibility of the obstetrician.

Participant: Doctor Yates, do you have any observations on carotid arteries?

Doctor Yates: Obstruction of the carotid arteries has been embolic in origin in all of my observations. I have one or two cases which seemed to be embolic from the placenta, just before or during the process of birth, but I have no evidence of traumatic, in my sense of traumatic, destruction of the carotid artery.

Doctor Page: It seems to me, from doing arteriograms in infants, that the collateral circulation through the circle of Willis is so completely ideal that it's hard to see how complete obstruction could occur.

Doctor Yates: The vertebrals are there for a purpose and that is mostly to supply the brain with blood. I don't think that the carotids could supply your lower brain stem very easily with the best circle of Willis in the world—the midbrain pons perhaps, but not the lower brain stem.

Doctor Ransohoff: I think that drawing conclusions from adult arteriosclerotic vascular disease is very valuable; certainly in a large series of patients who have "strokes" single-vessel disease is very rare. As you know, people can walk around with minor complaints of no significant neurological findings with only one vessel working out of the whole force. I would also agree with Dr. Page in the experience of operating on vascular lesions in very small infants. They have an ability to tolerate all kinds of occlusions of what one would normally accept as essential vessels, and not produce, at least, significant neurological deficits. Another problem is the difference between acute occlusion and, in the adult, progressive, chronic occlusion with a chance for collateral circulation.

Doctor Kling: Our experience in producing experimental arterial spasm in a monkey is that you must have close to 90 percent reduction in the caliber of the artery before you begin to affect flow whatsoever; it's pretty hard in major arteries to produce this degree of reduction, and these are major arteries that Dr. Yates is showing.

Doctor Churchill: If in the newborn infant one ties the middle cerebral artery, near the junction of the carotid, will that infant develop signs of hemiplegia that will persist and really develop cerebral softening, or will there be absolutely no deficit in the brain? This is the opinion I'm asking of you neuropathologists.

Participant: We don't do it very often.

Doctor Adams: Well, the collateral meningeal system is very well formed in late fetal life, after about the 5th month; these vessels are easily seen right on the surface and are probably larger in general than they are when the brain has been formed. As to whether we have any pathological example of an occlusion of the middle cerebral arteries after the circle of Willis with an infarct in the neonatal period—I can't remember one in our material, but certainly we have instances of infants older than this with an embolus or thrombus in this artery with a very extensive infarct.

Doctor Churchill: The reason for my question is strictly procedural, to get as a matter of record, that occlusion of a large cerebral vessel in the newborn or very young child, or even the fetus, can produce infarction.

Doctor Dodge: There is a study in progress under the direction of Dr. Ronald Myers which is possibly germane to the discussion. I was involved in some of the earlier studies with Dr. Adamson of New York in which both carotid vessels and other vessels in the neck were ligated in fetal macacas rhesus at about 80 to 90 days gestation. The fetuses were returned to the uterus and the animals permitted to go to near term.

The remarkable point is that despite this severe curtailment in blood supply to the fetal brain, the lesions were minimal. In one animal there was clearly a cyst involving the front portion of the brain bilaterally and some evidence of infarction in the second, but no lesions were visible in the majority of the animals so assaulted.

In a single animal in which this was carried out by Dr. Adamson and Drs. Lucey and James in the Oregon Primate Colony, they produced a lesion which was altogether reminiscent of the hydranencephalic brain which one sees in human infants. The catch is that this was an animal being bled to try to produce hydrops. It was a combination of vascular occlusion and severe anemia in the fetal animal. This I think may be an important observation, for it suggests to me that in such vascular occlusions there is probably some other associated factor involved in induction of such a lesion—a general decrease in circulation as a result of hypotension in the fetus, or a generalized decrease in oxygen tension for a period of time, or both.

REFERENCES

NORMAN, R. M.: Discussion on infantile cerebral palsies; pathology and etiology. *Proc. Roy. Soc. Med. 46: 627–631 (Aug) 1953.*

REACTION OF THE IMMATURE BRAIN TO INJURY

S. Mark Sumi, M.D.
Departments of Pathology (Neuropathology) and Medicine (Neurology)
University of Washington School of Medicine
Seattle, Washington

The reaction of the immature mammalian brain to injury differs considerably from that of the mature brain. In the immature brain, there is a rapid dissolution and complete resorption of the necrotic tissue, resulting in a smooth-surfaced cystic defect with little glial or connective-tissue scarring. In the adult brain the removal of necrotic tissue is slow and often incomplete, and healing is accompanied by the formation of a glial-fibrous tissue scar.

In our study, stab injury with a hook-shaped needle was produced in the brain of newborn rats and in older rats at various stages after birth.

Injury in Newborn Animals

For the first two to three days after injury in the newborn rat brain, the site of injury is marked grossly by a small amount of hemorrhage. Within the first 24 hours, many polymorphonuclear leukocytes and macrophages could be seen.

In the electron microscope the cortical edema surrounding the lesion was found to be largely extracellular, with marked distension of the extracellular space (fig. 1). There were no swollen astrocytic processes containing glycogen particles, characteristic of edema in the adult brain. Even around blood vessels, astrocytic processes were not seen.

But many microglial cells at various levels of activation were seen at this stage. The microglial cells were oval in shape and contained a large irregular nucleus with a small rim of cytoplasm. As phagocytic activity developed, lipid droplets appeared in the cytoplasm; mitochondrial and other organelles became more numerous, the cytoplasm more abundant, and the cell rounded. The nucleus then became displaced to the margin of the cell.

By the 2nd day most of the macrophages contained cell fragments as well as whole cells (usually erythrocytes and polymorphonuclear leukocytes), in addition to lipid droplets, dense bodies, and myelin figures (fig. 2). Some of the lipid droplets were surrounded by small dark granules varying in size from 40Å to 200

Part of this work was performed in collaboration with Dr. H. Hager, Max-Planck-Institut fur Psychiatrie (Deutsche Forschungstalt für Psychiatrie), Munich, Germany. Supported in part by Research Grants NB 07727 and GM 13543 and by training grants in neurology (NB 05067) and neuropathology (NB 05231) from the National Institutes of Health, U.S. Public Health Service.

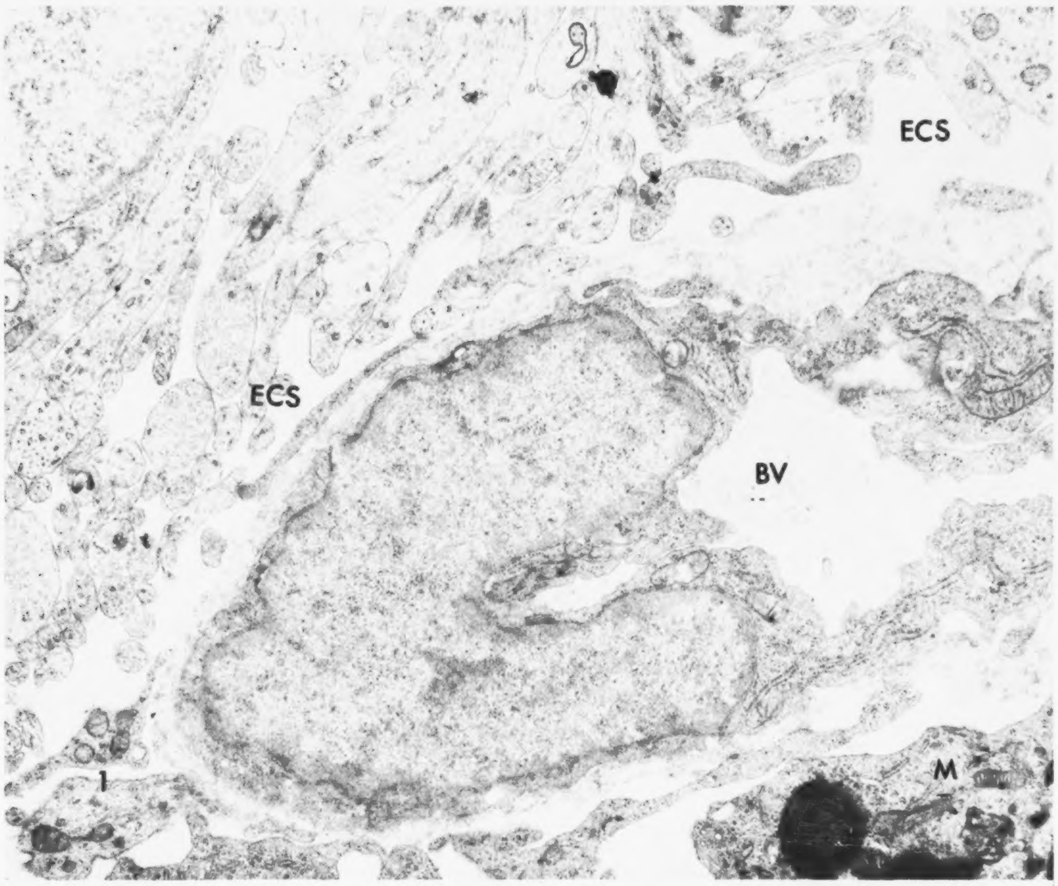


FIGURE 1—Cerebral cortex of newborn rat, 24 hours after injury. Edema is predominantly extracellular with distension of the extracellular space (ECS). No astrocytes are seen at this age, even around blood vessels (BV). Most of the processes are neuronal. A portion of a microglia cell (M) is seen. (Immersion fixation, glutaraldehyde, 400 mOs.) X 9,000.

Å. They resembled glycogen in that they became apparent only after lead staining, but their exact nature and significance was unclear.

By the 4th to 5th day a shaggy cystic defect was regularly found. In the light microscope the cyst wall was seen to be irregular, due to a heaping-up of cells, probably astrocytes (fig. 3). The cavity frequently communicated with the ventricle of the same side, and the junction between the cyst wall and the ependymal lining of the ventricle seemed quite sharp.

In the electron microscope (fig. 4) the cyst wall was formed by astrocytes that contained numerous organelles and a few filaments, and microtubules as well. From its surface, irregular processes projected into the cyst cavity. At this stage no basement membrane was present over these cells.

By the 3rd week, a smooth-walled cystic defect was present, often communicating with the ventricle on the one hand and the subarachnoid space on the other. Its resemblance to human porencephalic defects was often striking (fig. 5). The cyst wall was formed by a single layer of fibrous astrocytes and resembled the normal cortical surface in appearance (fig. 6). Immediately beneath this layer, this brain tissue appeared normal. Microglial cells were no longer seen. In the electron microscope (fig. 7) the single astrocytic layer was now covered by a base-

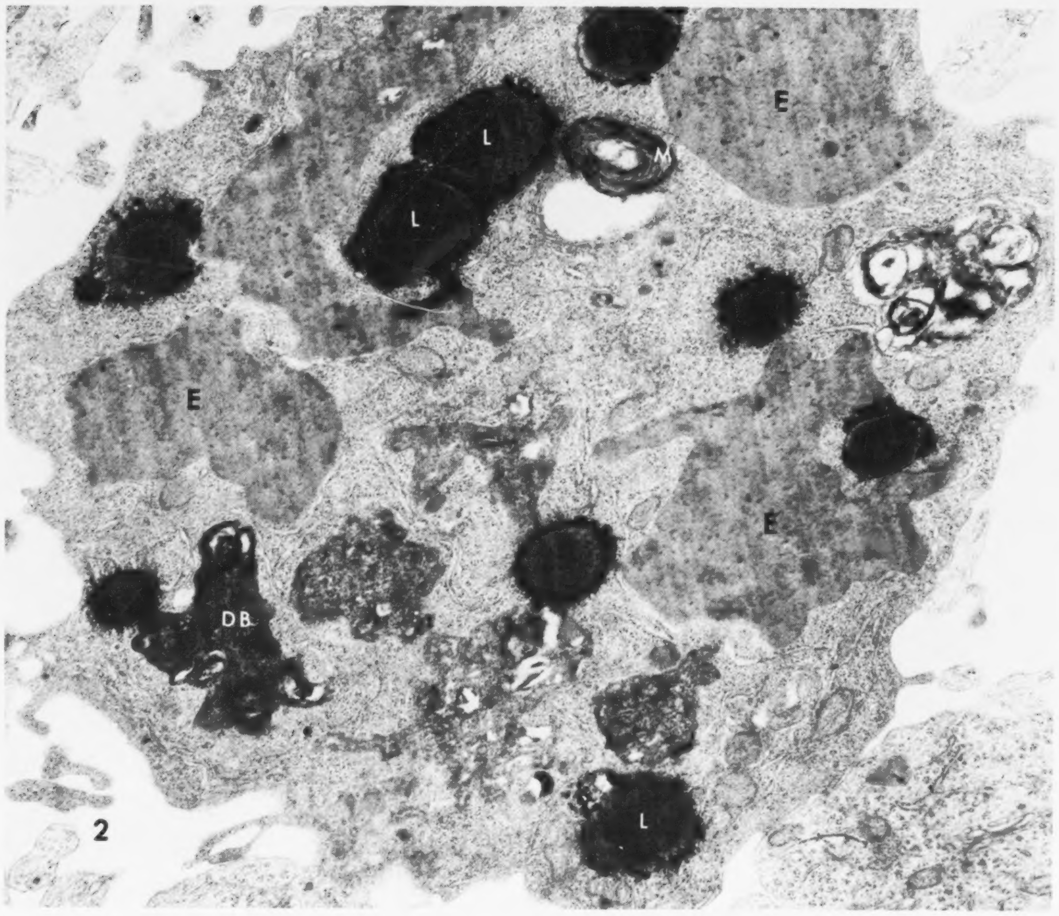


Figure 2—Activated microglia, 48 hours after injury, contains numerous red cell fragments (E), dense bodies (DB), lipid droplets (L), and myelin figures (MF). Lipid droplets are surrounded by dense granules. X 12,000.

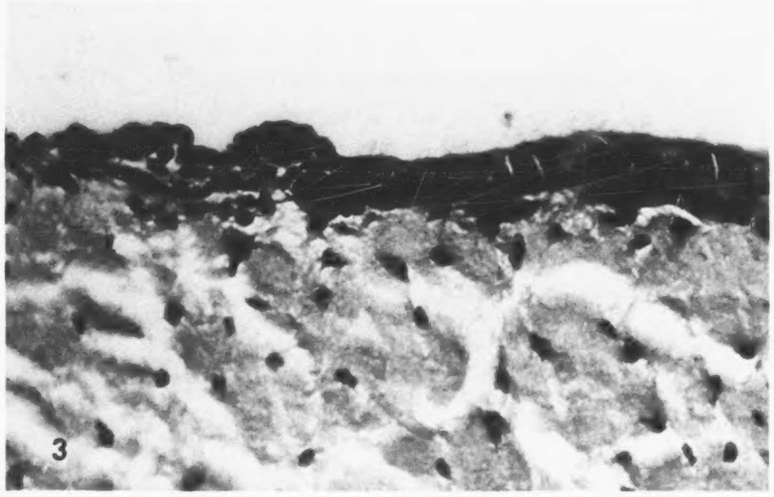


Figure 3—A sharp junction exists between cyst wall (left) and ependyma (right). Cyst wall is irregular, due to heaping up of cells, probably astrocytes. 5 days survival. H & E. X 150.

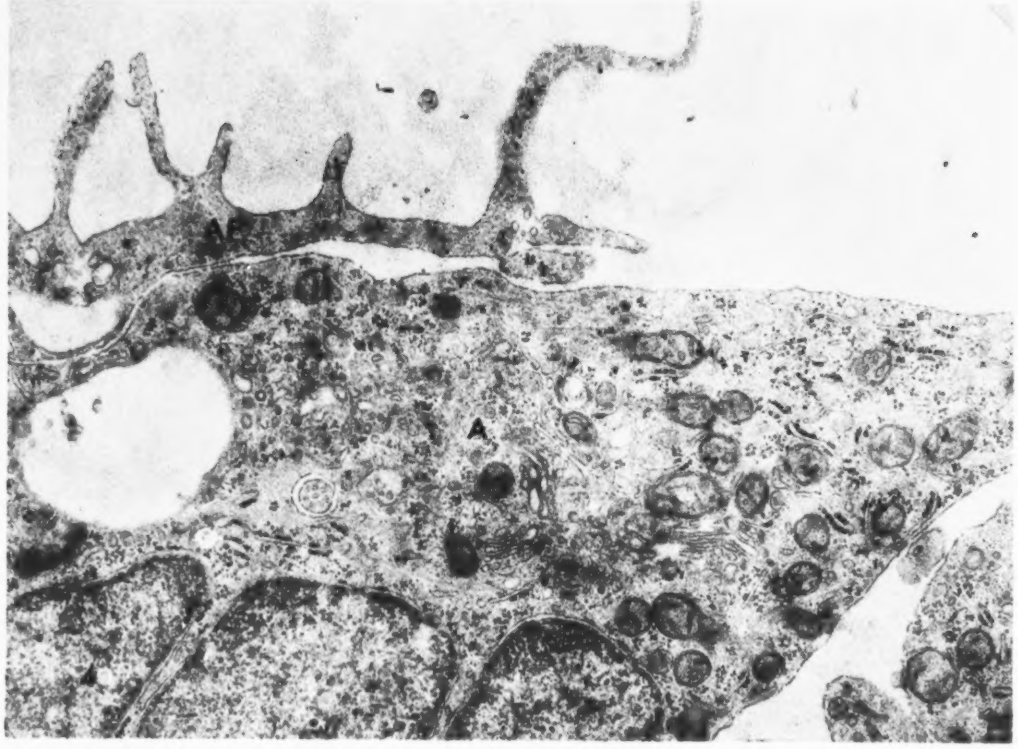


FIGURE 4—Cyst wall is formed by astrocytes (A) rich in organelles containing microtubules and a few fine filaments. Irregular processes (AP) arise from their surface. No basement membrane lining is present at this stage. 5 days survival. X 18,000.

ment membrane, and beyond this a few collagen fibrils were seen. Then there was a layer of pia-like cells. In places, the astrocytes possessed thin interdigitating processes. Normal-appearing neuropil was present directly beneath this astrocytic layer (fig. 8). This was the extent of the glial and mesodermal contribution to the healing process of this defect.

These findings are quite different from those seen in the mature brain (Table 1). The reasons for these differences have not been entirely clarified. The degree of scarring following injury appears to be related to the rate of removal of the necrotic tissue, and the lack of scar formation in the newborn animal may result from rapid removal of such tissue.

TABLE 1

	Newborn	*Mature*
Cortical edema	Mainly extracellular	Mainly astrocytic
Macrophage activity	Maximum in 2–3 days; disappears by third week	Maximum in 5–7 days; persists for many months
Cyst formation	Irregular cavity by 5–6 days; smooth-walled cyst by third week	Tissue resorption often incomplete
Scar formation	Minimal; cyst wall consists of pial cells and single layer of astrocytes	Dense astrocytic connective-tissue scar

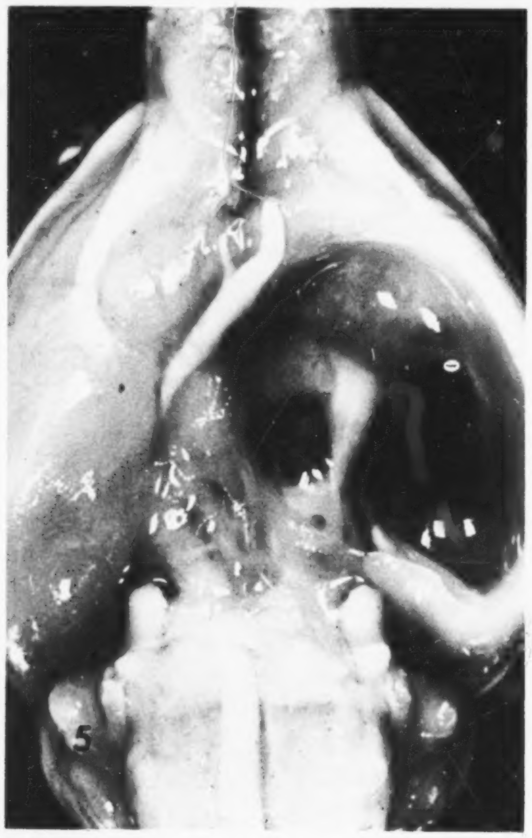


FIGURE 5—A large, smooth-walled cystic defect is often seen as an end result of the injury. Note its similarity to human porencephalic defects. Basal surface. 8 weeks survival.

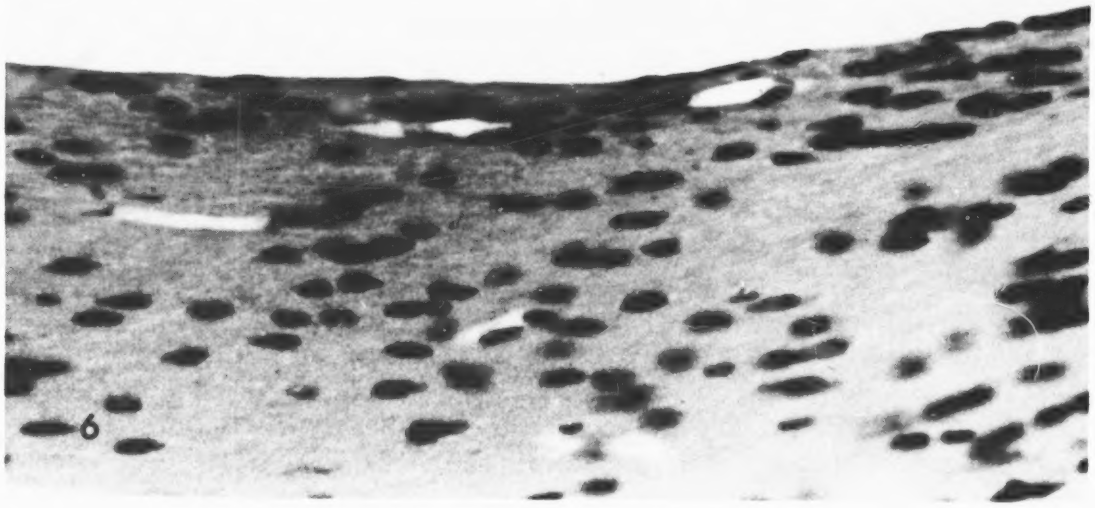


FIGURE 6—Cyst wall now consists of a single astrocytic layer and resembles the pial surface. No macrophages are present. 8 weeks survival. H & E. X 150.

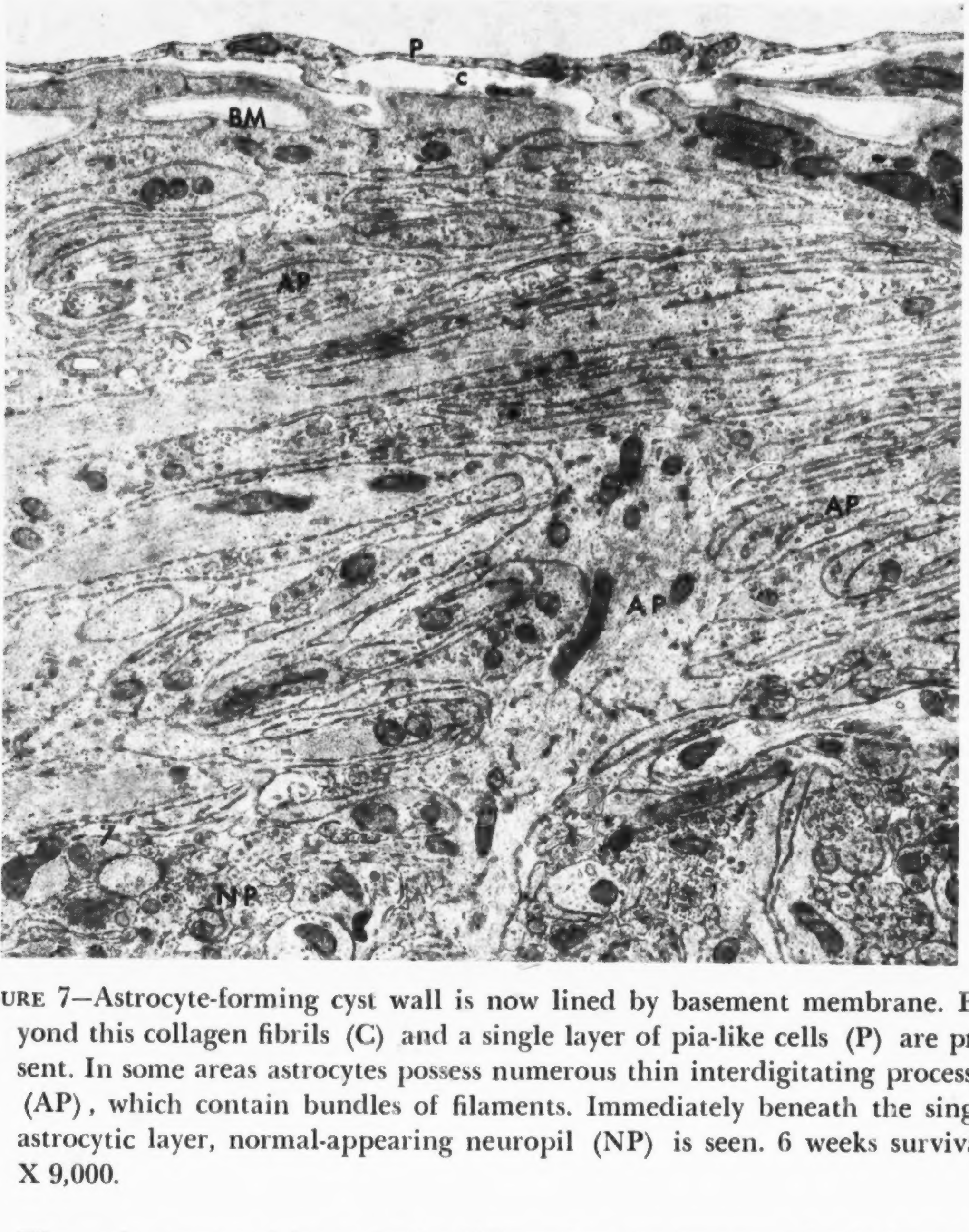


Figure 7—Astrocyte-forming cyst wall is now lined by basement membrane. Beyond this collagen fibrils (C) and a single layer of pia-like cells (P) are present. In some areas astrocytes possess numerous thin interdigitating processes (AP), which contain bundles of filaments. Immediately beneath the single astrocytic layer, normal-appearing neuropil (NP) is seen. 6 weeks survival. X 9,000.

The main structural features that differentiate the immature brain from the mature brain are listed in Table 2. The most obvious difference is the presence of myelin in the mature brain. Spatz contended that the myelin was difficult for the macrophages to digest, that a connective-tissue meshwork was formed to aid in this activity, and that this meshwork persisted as a permanent scar. The formation of dense glial connective-tissue scar in the cortex, where myelinated fibers are relatively few, and the failure of the connective-tissue scar to penetrate beyond the cortex following stab injury in the adult brain would appear to refute this theory. In addition, the astrocytic scar around the needle tract is usually more intense in the cortex than in the white matter.

The newborn brain has a higher water content than the mature brain. This may allow for a more rapid dissolution of necrotic tissue. In addition, the extracellular space in the immature brain appears to be much larger. Fixation with

TABLE 2

	Newborn	*Mature*
Myelin	Absent	Present
Water content	High	Low
Extracellular space	Large (variable, depends on osmolarity)	Small (relatively invariable)
Dendrites	Few	Many
Astrocytes	Few or absent	Present

the same glutaraldehyde solution, which gave a uniformly narrow extracellular space of 150 Å to 200 Å in the mature brain, resulted in a much wider extracellular space in the newborn brain (figs. 9, 10). Only between subpial astrocytes and ependymal and choroid plexus cells were narrow spaces consistently found. With maturation, this space became progressively smaller, but adult dimensions were attained only toward the end of the 2nd week of life. The narrowing of the extracellular space was accompanied by an increase in the number of neuronal and glial processes.

Not only was the extracellular space wider in the newborn animal, it was also very sensitive to slight changes in the osmolarity of the fixative. Fixation with a 400 mOs glutaraldehyde solution produced considerable narrowing of this space. Following injury, the extracellular space was wide even with this same fixative, suggesting that the increase in this space was due to the accumulation of edema fluid (fig. 11).

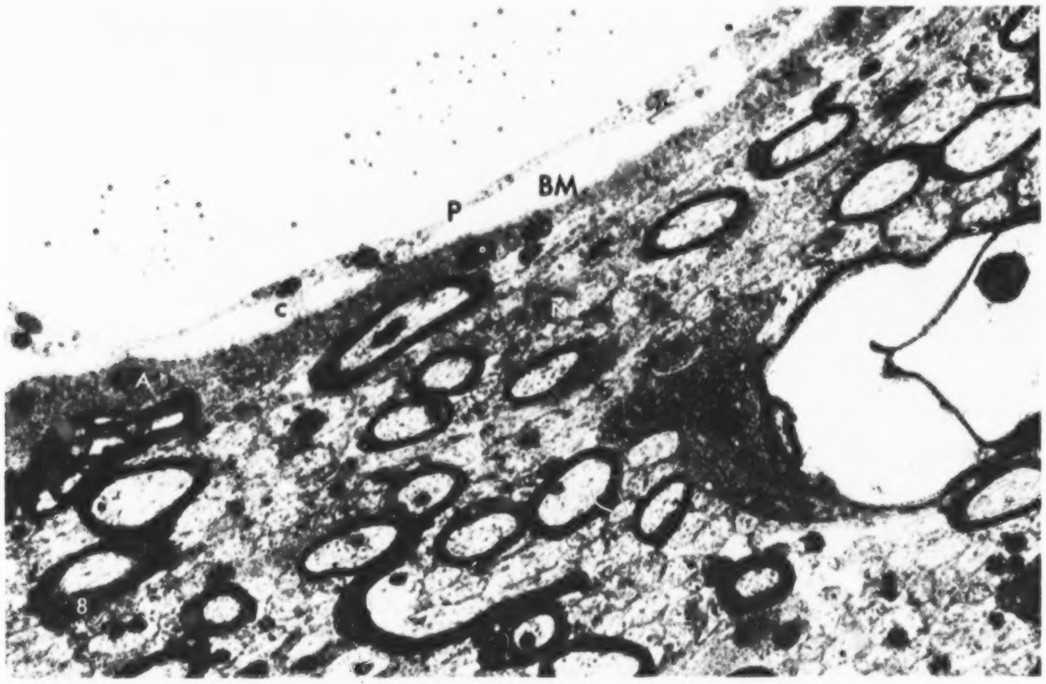


FIGURE 8.—Cyst wall, formed by pia-like cells (P) and single astrocyte layer (A). Immediately beneath it neuropil (NP) appears normal. Collagen fibrils (C), basement membrane (BM). 8 weeks survival. X 6,750.

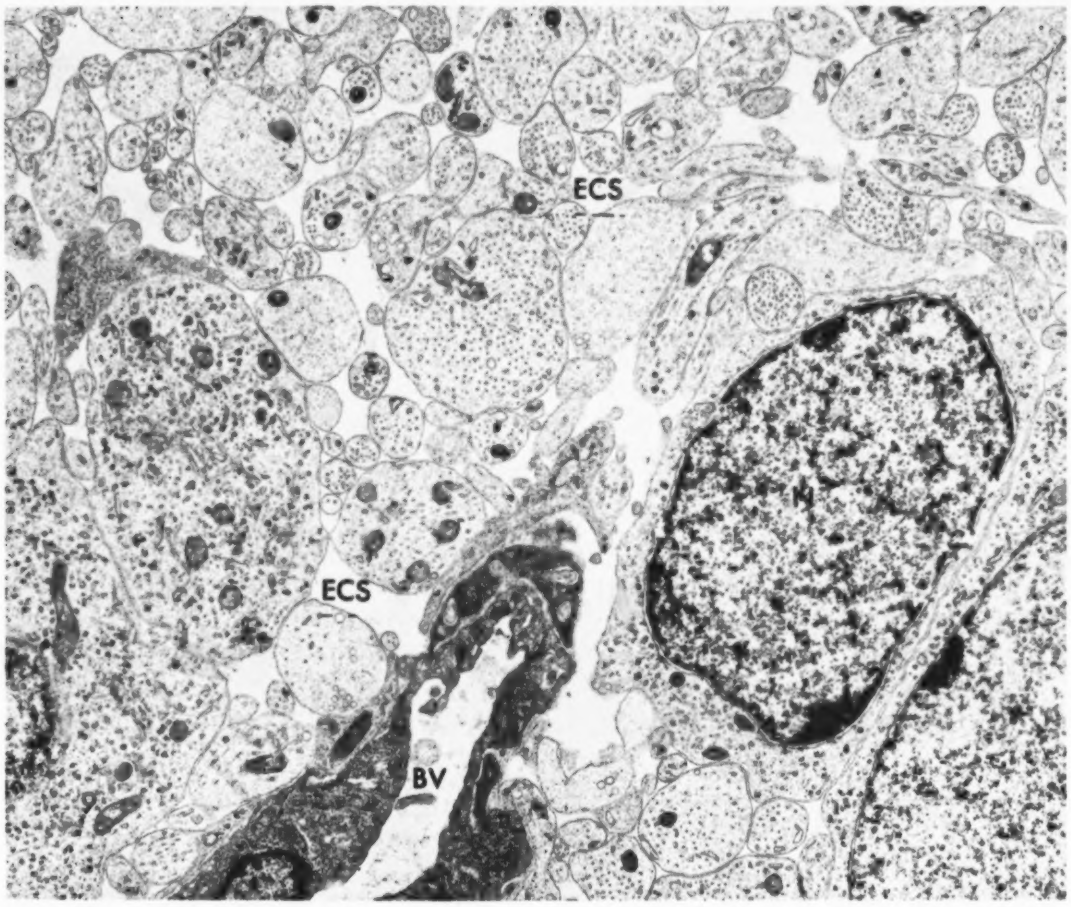


FIGURE 9—Normal cortex of 24-hour-old rat, fixed with 725 mOs glutaraldehyde solution. Note large extracellular spaces (ECS) and absence of astrocytic processes even around blood vessels (BV). Neuroblast (N). X 6,750.

It may be that the larger, more distensible extracellular space in the immature brain allows for greater ease in the inward and outward movement of macrophages, thus facilitating phagocytosis.

Another well-recognized feature of the immature brain is the paucity of astrocytes. Only in the subpial region could astrocytes be regularly found during the first week of life. This would account for the extracellular distribution of the edema fluid in the immature rat cerebral cortex, as opposed to the predominantly intracellular, astrocytic nature of cerebral edema, particularly in the cortex, in the mature animal, which is characterized by the swelling of the astrocytic processes and the accumulation of glycogen in these cells. The paucity of the astrocytes may also account for the lack of glial scarring following injury in the immature animal.

Injury in Maturing Animals

To clarify what morphological alteration with maturation is associated with the adult type of reaction, we are now studying the effects of injury at various ages after birth. The predominantly extracellular nature of posttraumatic cortical edema has been observed in animals injured as late as one week after birth,

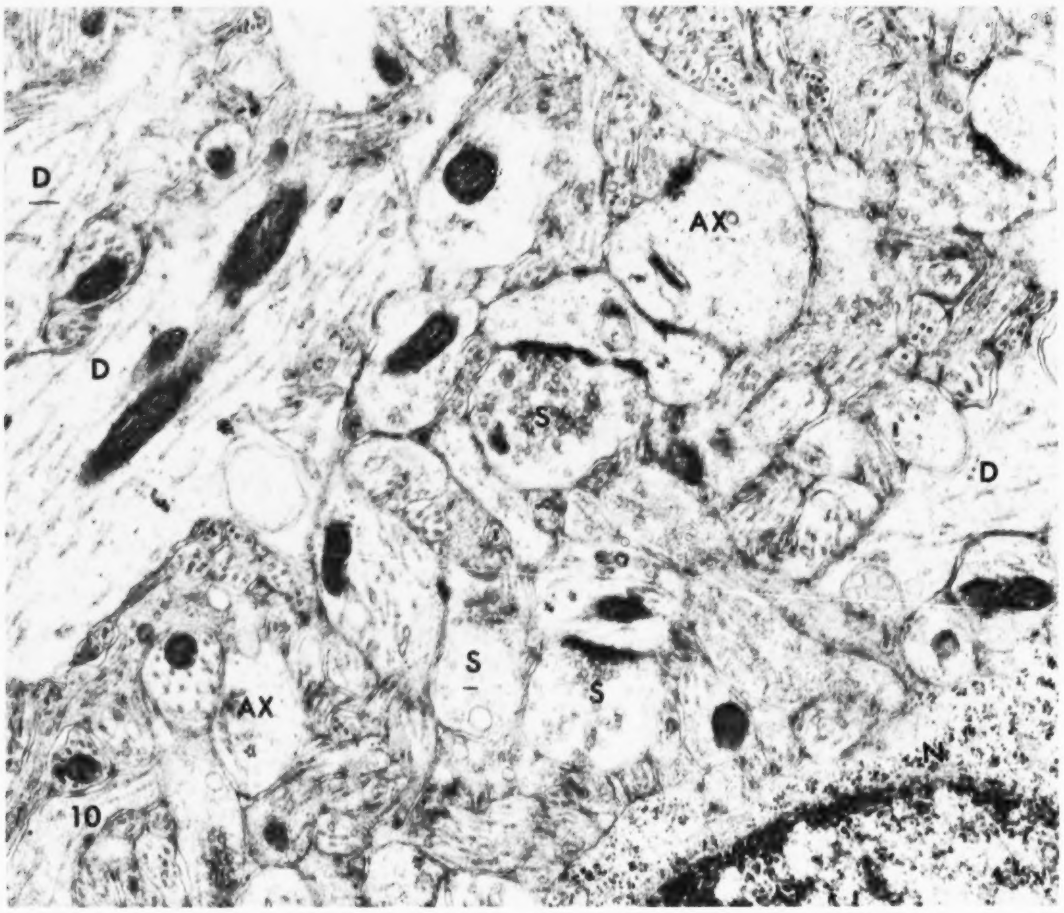


FIGURE 10—Normal cortex of 13-day-old rat, fixed with 725 mOs glutaraldehyde solution. Uniformly narrow extracellular space is now present. Dendrites (D), axons (AX), synaptic endings (S), neuron (N). X 19, 500.

and all these animals have shown healing by the formation of a smooth-walled cystic defect.

At 18 days of age, however, the early reaction is like that of the adult (fig. 12). Astrocytes appear in normal numbers, and the cortical edema is typical of the adult animal, with astrocytic swelling and accumulation of glycogen. The extracellular space remains narrow. After 10 weeks' survival, however, large cystic defects were again noted.

In the light microscope (fig. 13), the cyst wall in most animals was again quite smooth and resembled the cortical surface. Even after 10 weeks, however, hemosiderin-filled macrophages were still present in the cyst wall. In a few animals, the cyst wall was more irregular, with heaping up of some cells (probably astrocytes). Although we still do not have information as to the fine structural features of this cyst wall, even with the known presence of astrocytes, dense glial scarring characteristic of mature brain is not yet seen.

Conclusions

The main features of the reaction of immature brain to injury are the rapid mobilization and early disappearance of macrophages and the rapid dissolution

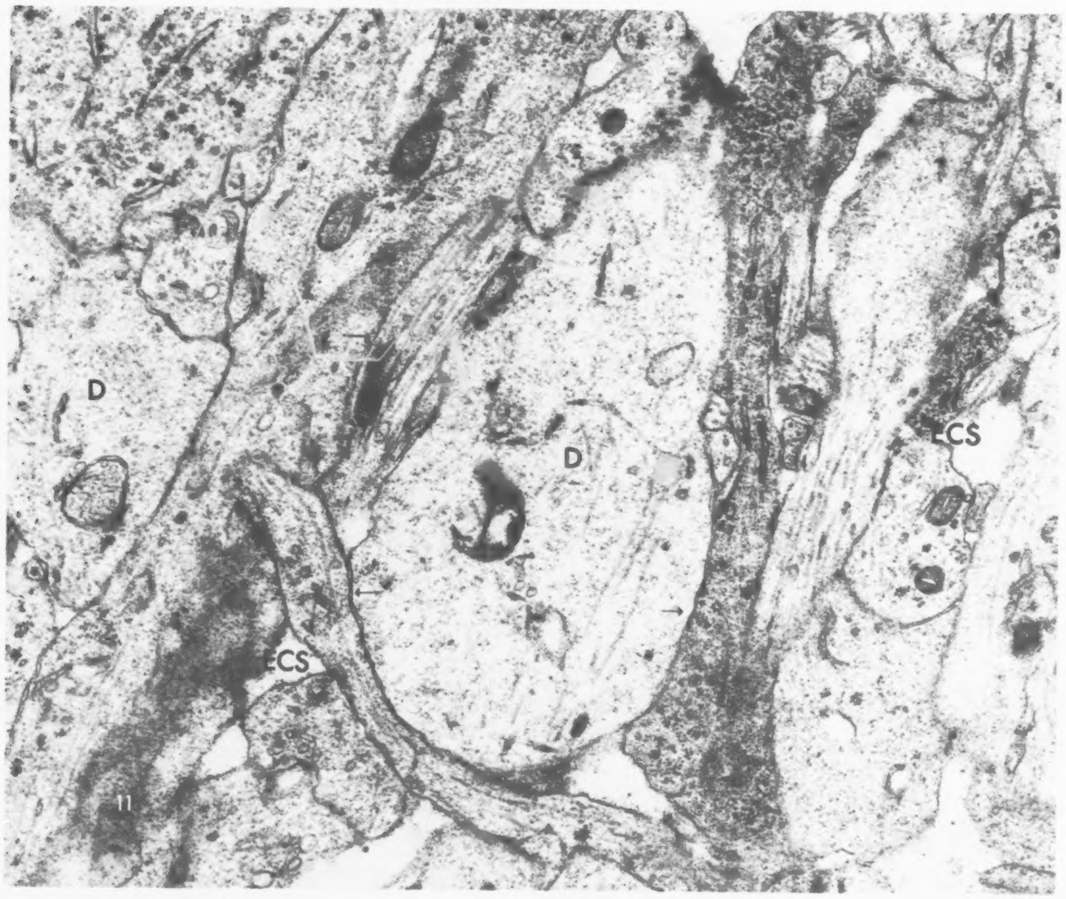


FIGURE 11—Cortex of 24-hour-old normal rat, fixed with 400 mOs glutaraldehyde solution. With this fixative the extracellular space is much narrower, but larger spaces (ECS) persist. Compares with fig. 1, which was fixed with the same solution. X 18,000.

and resorption of the necrotic tissue with healing by the formation of smooth cystic defect with minimal scarring (only a layer of pia-like cells and a single layer of fibrous astrocytes forming the cyst wall). The immature brain differs in several respects from the mature brain; which of these features is of greatest importance in determining the character of the reaction specific to the newborn brain is, as yet, unclear.

The final lesion in our experimental animal resembled the defect characteristic of porencephaly in man. When the greater portion of the cerebral hemispheres is absent and is replaced by a large cyst, hydranencephaly is the result. Both conditions are the result of symmetrical defects in the cortical mantle. Considerable controversy exists as to the origin of these lesions in man. Some ascribe them to infarction occurring in early gestation—a destructive process—whereas others attribute similar lesions to a failure of proper development of the cerebral mantle—a malformation. One basis for differentiating between these two pathogenetic mechanisms has been evidence in the lesion of a destructive process, such as the persistence of gitter cells, calcifications, and gliosis. If such findings were absent, the defect was attributed to a malformation. We would suggest that the presence or absence of such evidence of a destructive process may be related only

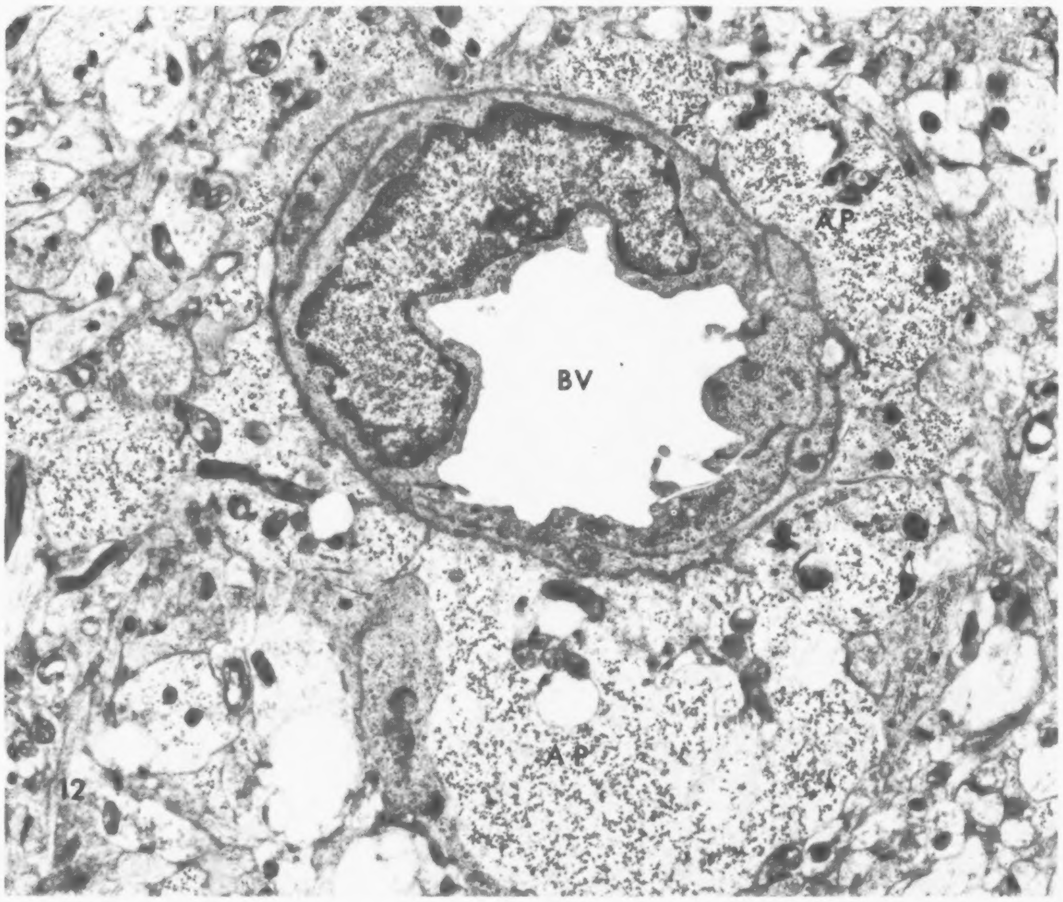


FIGURE 12—Trauma in 18-day-old rat, 24 hours after injury. In the cortex numerous swollen astrocytic processes (AP) containing glycogen granules are present. The extracellular space maintains its uniform, narrow dimensions. Blood vessel (BV). X 9,000.

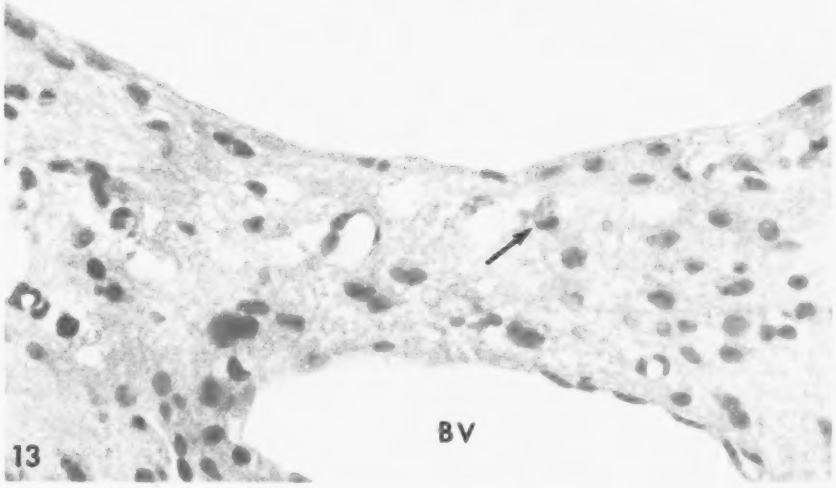


FIGURE 13—Trauma in 18-day-old rat, 10 weeks survival. Cyst wall is smooth and formed by single layer of astrocytes. Hemosiderin-containing macrophages ↑ persist in the cyst wall. H & E.X. 300.

to the stage of gestation at which tissue destruction occurred. The absence of such lesions cannot be used as evidence for a primary developmental defect.

DISCUSSION

Doctor Black: It is quite correct, I think, that cavitation is very much more prominent in the neonatal brain as a rule than it is in older organs. My guess would be that after you have looked through all those possible explanations there is only one that makes any sense, and that is that a mass of debris at this age is nothing but water, a few cells and straggling processes. The massive debris in a 2-year-old brain is full of myelin fragments and stuff. In both instances it has to be removed not entirely by phagocytosis, but partly by resorption in some way, and the excitation of the macrophage reaction at this age is much less, as a general rule, for clearing all of this out.

Doctor Hicks: We have made all kinds of lesions in newborn rats, some fetuses and older stages. The size of the lesion you make is very important. If you make a very delicate slice through a whole hemisphere, using a very fine wire as a knife and approximate the two sides with or without removal of part of the cortex, it's very difficult later on. In cats, which are perhaps more like a human being in this stage of development, you may see almost no gliosis.

As best we could tell from the material, the appearance of various cellular elements was parallel at the different ages. The lesion of a fine needle or the lampblack used to identify the needle track did excite an astrocytic response. There was no extensive gliosis in the neonatal or in the older animals either because of the nature of the lesion.

Participant: The site of the lesion is also important. More intense reactions are noted in the depths of the lesion which may be dependent on the greater vascularity and myelinization of the brain stem tissue.

REFERENCES

Bakay, L. and Lee, J. C.: *Cerebral Edema*. Springfield, Ill.: Charles C Thomas, 1965.

Barlow, C. F., et al.: Extracellular brain space measured by S^{35} sulphate. *Arch Neurol 5: 102–110 (July) 1961.*

Bondareff, W., and Pysh, J. J.: Distribution of the extracellular space during postnatal maturation of rat cerebral cortex. *Anat Rec 160: 773–780 (April) 1968.*

Brizzee, K. R., and Jacobs, L. A.: The Glia/neuron index in the submolecular layers of motor cortex in the cat. *Anat Rec 134: 97–105 (May) 1959.*

Donaldson, H. H., cited by Sperry, W. M.: The biochemistry of the brain during early development. in *Neurochemistry: The Chemistry of Brain and Nerve,* (ed.) Elliott, K. A. C., et al. Springfield, Ill.: Charles C Thomas, 1955, pp 243–244.

Gudden, B.: Experimentaluntersuchungen über das peripherische und centrale nervensystem. *Arch Psychiat Nervenkr 2: 693–723, 1870.*

Hager, H. Elektronenmikroskopische befunde zur cytopathologie der abbau-und abräumforgänge in experimentell erzeugten traumatischen hirngewebsnekrosen. *Naturwissenschaften 17: 427–28, 1960.*

Hager, H.: Elektronenmikroskopische befunde zur cytopathologie der astrocyten im zentralnervensystem der säugetiere: reaktive veränderungen und gliöse defektdeckung. *Proc V Internat Congress for Electron Microscopy,* Philadelphia, New York: Academic Press, vol. 2, SS–9, 1962.

Hager, H., Luh, S., Ruščaková, D. and Ruščák, M.: Histochemische, elektronenmikraskopische und biochemische untersuchungen über glykogenanhäufung in reaktiv veränderten astrozyten der traumatisch lädierten säugergrosshirnrinde. *Z Zellforsch 83: 295–320, 1967.*

Hicks, S. P., and D'Amato, C. J.: Cell migrations to the isocortex in the rat. *Anat Rec 160: 619–634 (Mar) 1968.*

Hirano, A., Zimmerman, H. M., and Levine, S.: The fine structure of cerebral fluid accumulation. VII. Reactions of astrocytes to cryptococcal polysaccharide implantation. *J Neuropath Exp Neurol 24: 386–397 (July) 1965.*

Klatzo, I.: Presidential address. Neuropathological aspects of brain edema. *J Neuropath Exp Neurol 26: 1–14 (Jan) 1967.*

Lange-Cosack, H.: Die hydranencephalie (blasenhirn) als sonderform der grosshirnlosigkeit. I. Anatomischer teil. *Arch Psychiat 117: 1–51, 1944.*

Marburg, O., Rezek, Ph. R., and Marks, M. B.: Porencephaly. II. Studies in phlebothrombosis and phlebostasis. *J Neuropath Exp Neurol 4: 43–58 (Jan) 1945.*

Penfield, W., and Buckley, R. C.: Punctures of the brain: the factors concerned in gliosis and cicatricial contraction. *Arch Neurol Psychiat 20: 1–13 (July) 1928.*

Spatz, H.: Uber die vorgänge nach experimentellen rückenmarksdurchtrennung mit besonderer berücksichtigung der underschiede der reaktionsweise des reifen und des unreifen gewebes nebst beziehungen zur menschlichen pathologie. (Porencephalie und syringomyelie.) *Nissl-Alzheimer Histolog Histopathol Arb, E B 49–364, 1921.*

Sumi, S. M.: Extracellular space in the developing rat brain (in preparation).

Torack, R. M., Terry, R. D., and Zimmerman, H. M.: The fine structure of cerebral fluid accumulation: I. Swelling secondary to cold injury. *Am J Path 35:1135–1147 (Nov–Dec) 1959.*

Vernadakis, A., and Woodbury, D. M.: Cellular and extracellular spaces in the developing rat brain. *Arch Neurol 12: 284–293 (Mar) 1965.*

Wilson, R. B.: Brain repair. *Arch Neurol Psychiat 15: 75–84 (Jan) 1926.*

Yakovlev, P. I., and Wadsworth, R. C.: Schizencephalies. A study of congenital clefts in the cerebral mantle. I. Clefts with fused lips. *J Neuropath Exp Neurol 5: 116–130 (Apr) 1946.* II. Clefts with hydrocephalus and lips separated. *5: 169–206 (July) 1946.*

EFFECTS OF REMOVAL OF PARTS OF THE EARLY INFANT RAT'S BRAIN ON ITS MORPHOGENESIS AND FUNCTIONAL DEVELOPMENT

SAMUEL P. HICKS, M.D. AND CONSTANCE J. D'AMATO, B.S.
Department of Pathology
University of Michigan Medical Center
Ann Arbor, Michigan

An organism builds its nervous machine with a genetically fixed program, but the program has enormous flexibility. This enables the nervous system on the one hand to redirect its building processes to restitute losses from injury and on the other to be shaped structurally and functionally by its own periphery and the environment, as part of the normal developmental process.

This later "embryonic learning" process is illustrated in classic experimental amphibian embryology when an early hind limb is transplanted to replace a forelimb. As the limb becomes connected to the central nervous system it sends a message, apparently by molecular transmission along the nerves, saying, "Wire me up, I'm ready for action." Within limits of its repertoire, the nervous system may oblige, redirecting the building of its forelimb circuitry to run a hind limb appropriately. But it is not always obliging and may make both fore and hind limb circuitry, telling the limb, "You'll have to accept both; your behavior will be hybrid."

Though mammalian limb buds have not been transplanted this way, our experiments with radiation as an experimental mammalian embryological tool have shown that regulative processes and the capacity to restitute injury are basically similar in mammals and similar vertebrates. We have shown that a mammalian neural fold or early spinal cord, retina, or limb can recover almost completely from devastating damage at some stages, although malformative disaster may result at other stages when certain processes are disturbed. That some profound readjustments, including central-peripheral interactions, may go on in mammals is illustrated by a man who was born without a cerebellum and lived out his life with adequate motor function, and another who was quite bright and normal but who had no fornix, a rudimentary hippocampus, and little corpus callosum. The periphery in the first man must have demanded of the brain during development, "Wire me up whether you've got a cerebellum or not." Which it did.

There are many examples in animals and man to support the observation that a young organism can sometimes sustain deficits and alterations of the nervous system and compensate for them functionally remarkably well, whereas an organism with a comparable deficiency acquired later in life cannot.

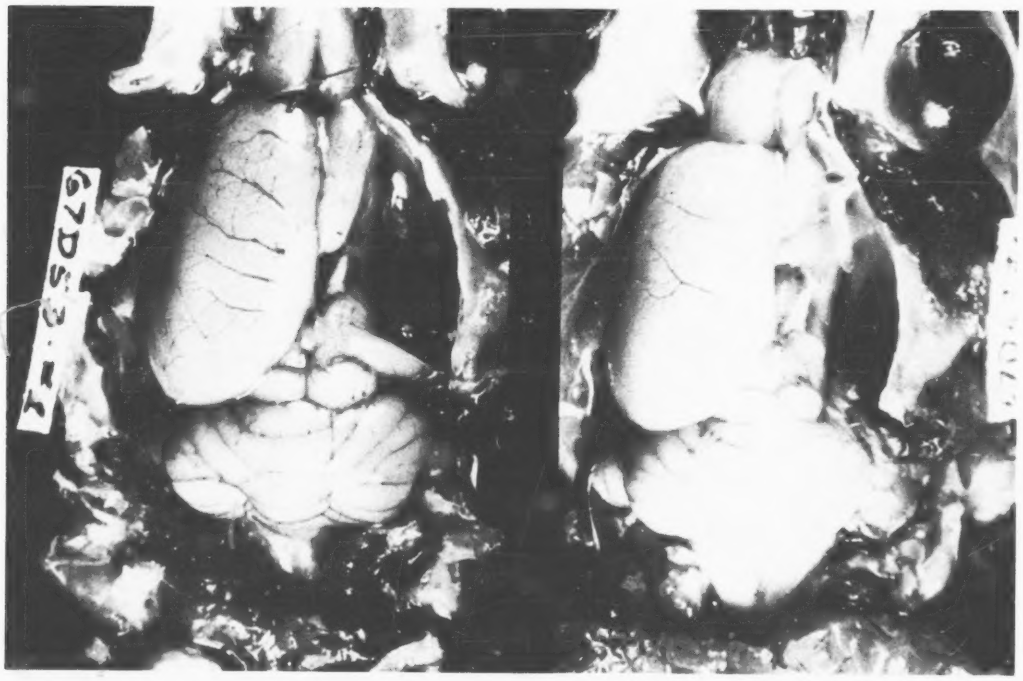


Figure 1—Brains of two adults rats (6 and 5 months of age) following near-total hemispherectomy when rat was newborn.

The rat at the time of birth still possesses "plasticity" that can be explored experimentally; its cerebellum has scarcely begun, and its isocortex and, especially corpus striatum have still to receive part of their complement of neurons and glia, as our tritiated thymidine monitored studies of cell migrations have shown. We have removed parts of the brain in rats during the first 24 hours after birth, at other stages, and at maturity, and have followed the animals' behavior, especially certain reflexes and motor behavior, using the slow-motion moving pictures as one form of record. We have studied the histologic morphogenetic changes that occur. The operations have included unilateral and bilateral removal of frontal (motor), somaesthetic, and visual regions of isocortex; nearly complete hemispherectomy rostral to the tentorium; hemispherotomy; and cerebellectomy. In infant rats only we have done superior colliculectomies and attempted to remove the anterior striatum. These experiments are in various stages of development; here are some of our findings.

Unilateral or bilateral removal of frontal cortex leads to failure to form in infants or degeneration of (in mature animals) a major portion of the fibers in the pyramidal tract. There is no visible impairment of gait in infant operates, but there may be in adults, though it may be due to encroachment on the adjacent somaesthetic cortex. Rats 14 days or older promptly lose their lateral tactile placing reaction on one side after removal of the opposite somaesthetic cortex. One- and 5-day-old rats so treated show no sensory or motor impairment until 17 days old when the tactile placing disappears in a couple of days. Hopping, stepping, and visual placing are umimpaired, or are very transiently affected in adults; forward tactile placing is variably affected. In both mature and infant operates there is considerable atrophy of the ventral and lateral thalamus. The behavior of hemispherectomized 1-day-old and mature rats, in respect to these re-

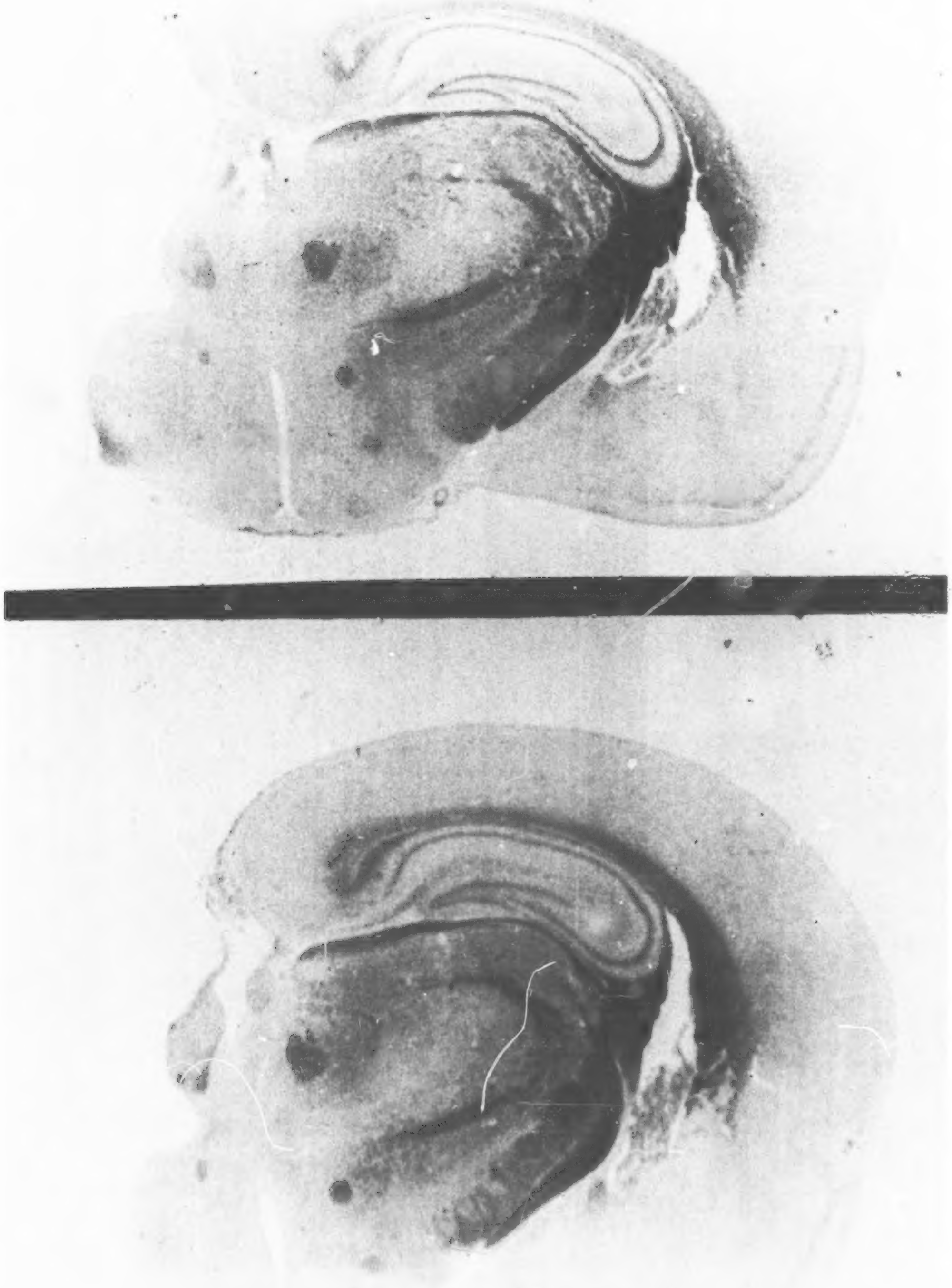


FIGURE 2—Mid-frontal sections of the brains of two rats near-totally hemispherectomized when rat was newborn.

sponses, parallels the behavior of operates whose somaesthetic cortexes have been removed.

Thus the infant rat has a mechanism, unidentified, for lateral tactile placing that can serve both sides of the body. But it is usurped by a cortical-thalamic mechanism at the time the rat is acquiring a mature pattern of locomotion. However, four of 15 rats, 1-5-days old, deprived of somaesthetic cortex, retained their tactile response, although the cortical defect and thalamic reduction seemed similar to that of functionally deficient animals. Further study is needed to see whether this represents the advantage of youth over age in reaction to brain damage, and if so, how it came about.

Rats hemispherectomized at one day (15 have been done with no losses; some are now 7 months old) let the feet contralateral to the ablation slip off the edge of the running track during the first few weeks after they begin to run; but this improves and their gait becomes nearly normal. Hemispherectomized mature rats have little difficulty this way. The infant operates readily jump from one platform to another (8 x 14 cm) from around 3 weeks on, reinforcement at first being the jumping, handling, or returning to a home cage (fig. 3). They gauge visually and jump accurately distances randomly varied up to 40 cm when they are a few weeks old. (Food, under deprivation, becomes a more effective reinforcement after 2 or 3 months; the operates learn the task more slowly and usually need to be hungrier to take a given amount of food in a limited time. Adult operates show comparable behavior.)

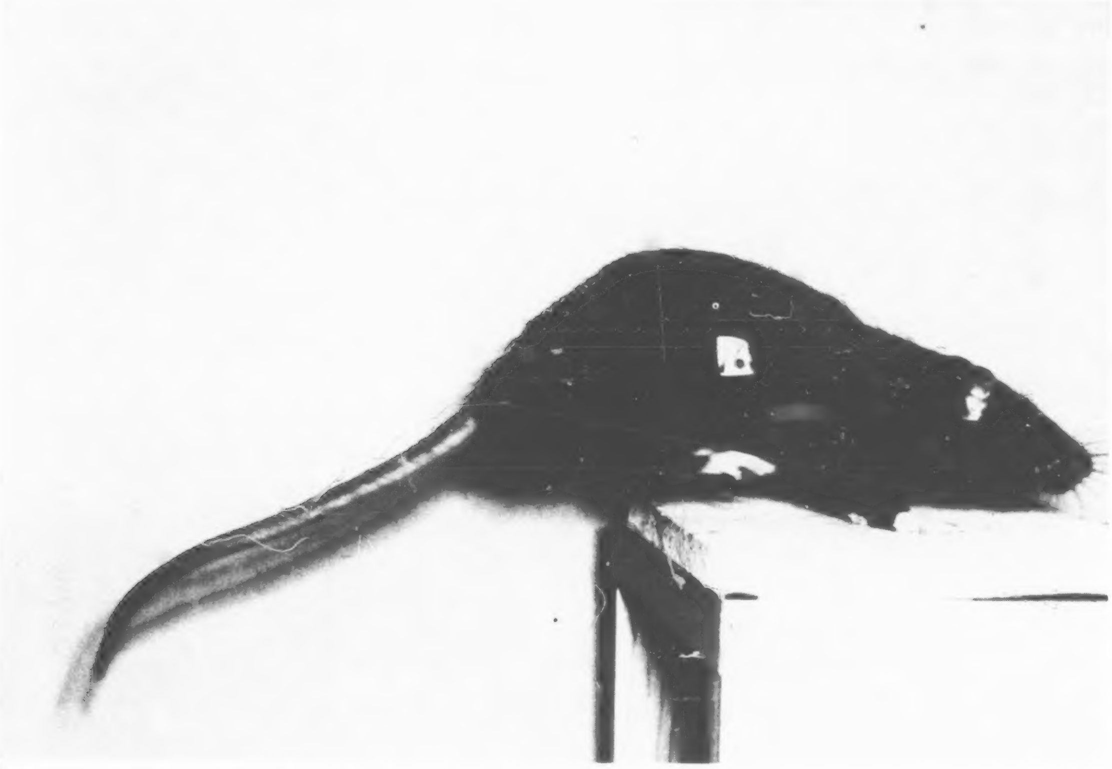


FIGURE 3—Rat near-totally hemispherectomized when rat was newborn jumping accurately from one platform to another.

Rats "cerebellectomized" at 1 or 5 days begin to show unsteadiness at 14 days and tend to fall at 17. As they mature (some are now 4 months old) they can stand briefly and walk and run very short distances. These activities are interspersed with frequent episodes of falling and spastic extension of the limbs and sometimes twisting of the trunk. They manage to brace themselves to get food and water; they romp and sham fight vigorously, though often grotesquely, with their normal and abnormal littermates. "Cerebellectomy" has to be qualified here as being variably incomplete. At one day, for example, the cerebellum is scarcely more than an anlage, and it is difficult not to leave a little behind from which a part of the mature organ arises. Usually, much of the central cerebellum and fastigial nuclei are absent.

We have little as yet to report on the animals with visual cortices or colliculi ablated. Visually guided jumping and pattern discrimination are being tested.

The isocortex has received virtually no glia in the newborn rat, and operative defects whose margins can appose heal without gliosis. Later there may be only the disturbed architecture to indicate where the lesion was, the adjoining regions having melded. Our experiments with hemispherotomy, coronal section through nearly the whole hemisphere, or both at the level of the striatum, or more caudal, are designed to show how much anatomic fiber growth and function is restituted across the cut. It is remarkable how little bleeding, disruption of blood supply, and residual damage there is in these lesions.

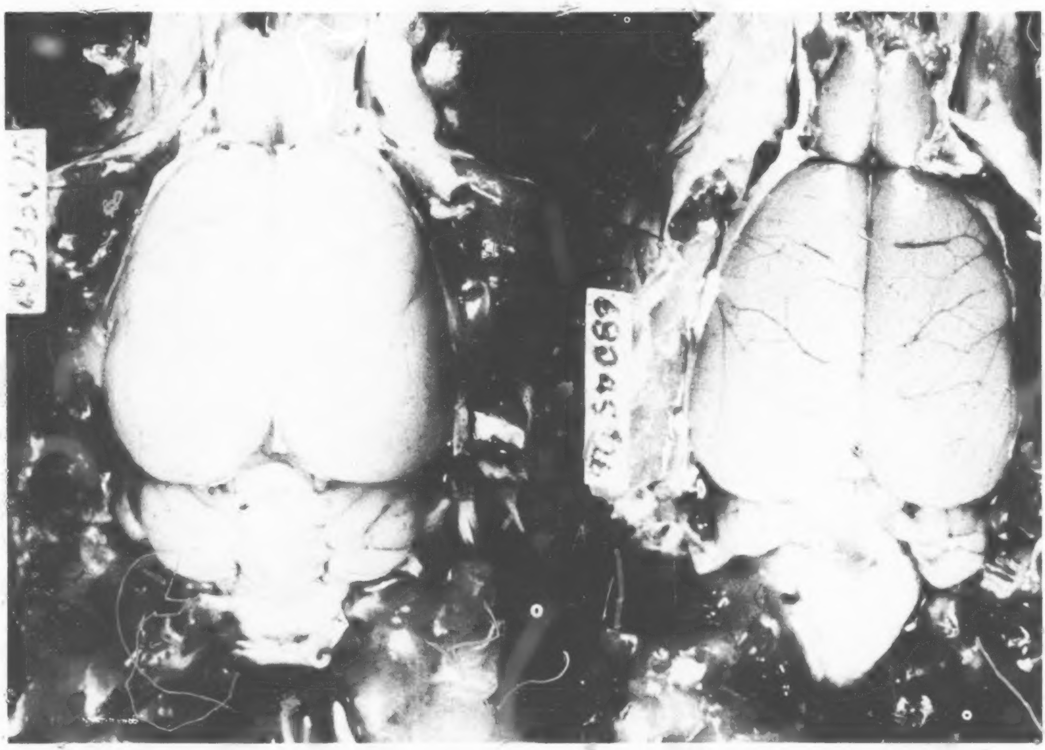


FIGURE 4—Brain of adult rat near-totally cerebellectomized at 5 days of age (right) compared with a normal (left).

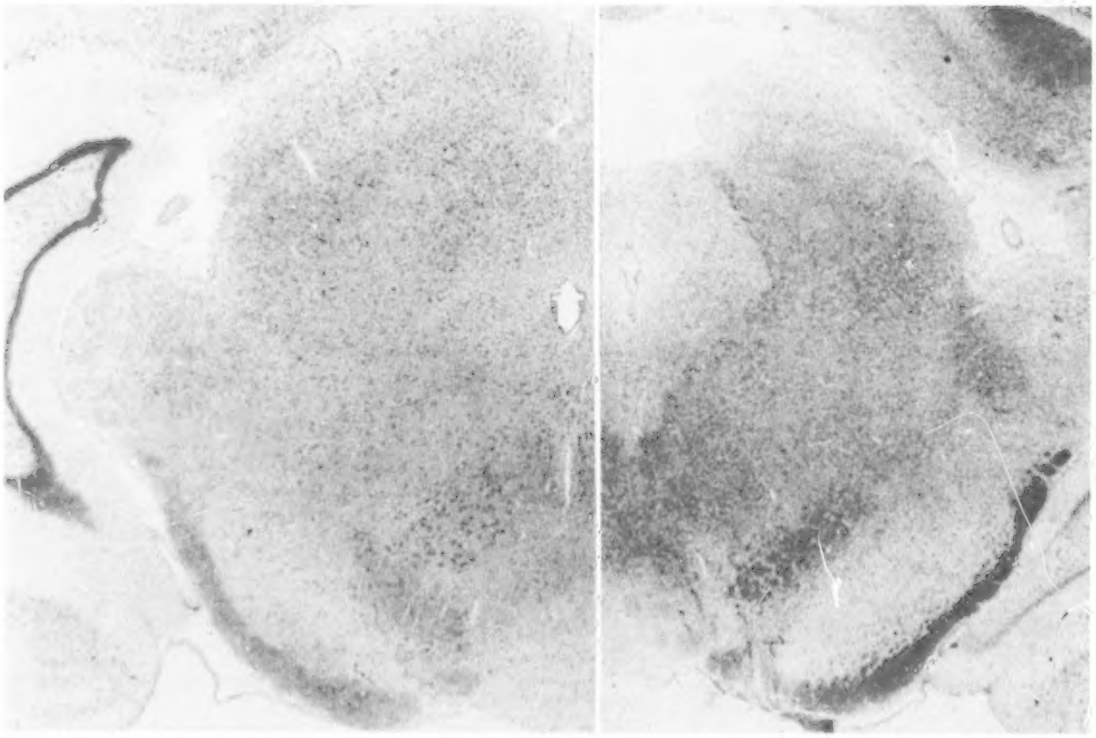


FIGURE 5—Section of midbrain (right) of young mature rat whose superior colliculi were near-totally removed when rat was newborn compared with normal (left).

THE EFFECT OF CEREBRAL ABLATION IN INFANT MONKEYS ON MOTOR AND COGNITIVE FUNCTION

ARTHUR KLING, M.D.
Brain Research Laboratory
University of Illinois College of Medicine
Chicago, Illinois

It is by now well-established that a variety of sensory and motor functions may be spared after lesions of the cerebral cortex if the damage is sustained early in life, particularly if the lesion is limited to one hemisphere. Kennard demonstrated in the monkey that the degree of paresis and spasticity resulting from lesions of the motor cortex or hemispherectomy is age-dependent. She found that if the injury was sustained prior to 7 months of age considerable sparing or restitution of motor function occurred. However, after 7 months similar lesions resulted in more prolonged paresis. She concluded that the earlier the age of operation the less the eventual motor dysfunction.

Another important finding in her experiments was that extension of the motor cortex lesions rostrally or caudally to include prefrontal or sensory areas resulted in less restitution of motor function. A number of other experiments in our laboratory and elsewhere have demonstrated sparing of a variety of functions after neonatal lesions of cerebral cortex and limbic structures. While much has been learned from these studies, there has been little progress in understanding the neural mechanisms underlying this phenomenon.

For example, in most instances the infant operates have not been observed over a long enough period to determine whether the functional sparing holds up into maturity or whether deterioration eventually occurs. It has also been assumed that the sparing or restitution of function which occurs after unilateral lesions or hemispherectomy is a consequence of the other hemisphere taking over the function of the injured side. This has been postulated for motor function and for the development of speech in man.

A more difficult problem exists in explaining the restitution of function after bilateral lesions. Kennard has postulated that areas adjacent to the lesion may be responsible since extending lesions of motor cortex to include other areas accentuates the deficit. While subcortical areas have been implicated in contributing to the restitution of function after cortical lesions, no direct evidence has been presented to substantiate this view.

Another aspect of this problem lies in determining not only what functions are spared after early lesions, but also those which are not. This approach may

1961

shed light on both the limits of sparing and the neural systems which may be involved in this phenomenon.

The purpose of this report is to review some recent experiments from this laboratory directed toward a further understanding of these problems. While a variety of observations have been made on the subjects to be discussed, this report will deal primarily with the area of cognitive function and its relation to somato-motor development.

Among the most consistent disturbances in cognitive function after a localized cortical lesion in the monkey is that which occurs after a bilateral abalation of frontal granular cortex. While these preparations can perform adequately on a variety of visual discriminations, they are unable to master delayed response or delayed alternation.

The basic requirement in the delayed response task is for the monkey to remember under which of two identical plaques a bit of food was placed. After the monkey is given an opportunity to observe where the bait was placed, an opaque screen is raised and the monkey is required to choose the correct plaque for a reward. Normal monkeys over 6 months of age begin to solve this problem up to and including the 40-second delay period. Another task that the frontal monkey cannot do is delayed alternation which requires that the monkey remember on which side the previous correct response was made and go to the opposite side on the next trial, in a sense inhibiting the natural tendency to return to the side of the previous reward.

Along with the inability to learn the above task monkeys with bilateral frontal cortex lesions typically display hyperactivity and distractability. The hyperactivity is especially noticeable during testing or during heightened emotional states. In adult operates the hyperactivity occurs immediately after operation and tends to diminish in intensity over a period of a year.

In our first experiment we compared the effects of bilateral ablation of frontal granular cortex in four infant monkeys operated between the 1st and 34th postnatal day with three who were approximately 3 years old (fig. 1). All infants were born in the laboratory while the adults were of feral origin. Three of the infant operates were returned to their respective mothers within 24 hours after operation. One was artificially reared in an incubator. The maternally reared subjects were separated at 5 to 6 months of age close to the initiation of testing. Adult operates began testing approximately 2 months after surgery.

Three of the infant operates were killed at approximately 1 year of age, after completing the aforementioned test series. Up to that age none of these developed the hyperactivity and circling behavior which was characteristic of the adult operates. On gross observation they were indistinguishable from normal yearling monkeys. One infant operate was observed for 2 years and was retested on the delayed response beginning at 18 months. In contrast to his superb performance at 10 months of age, he could do no better than 5 seconds after 18 months of age. In addition he displayed the hyperactivity and distractability characteristic of adult operates.

The tests on the early frontal monkeys showed no difference between the two groups on color discrimination or delayed alternation. On delayed response, however, there was a marked difference in the early versus the late lesions. The best that a late lesion was able to do was 5 seconds. Of the four early frontal mon-

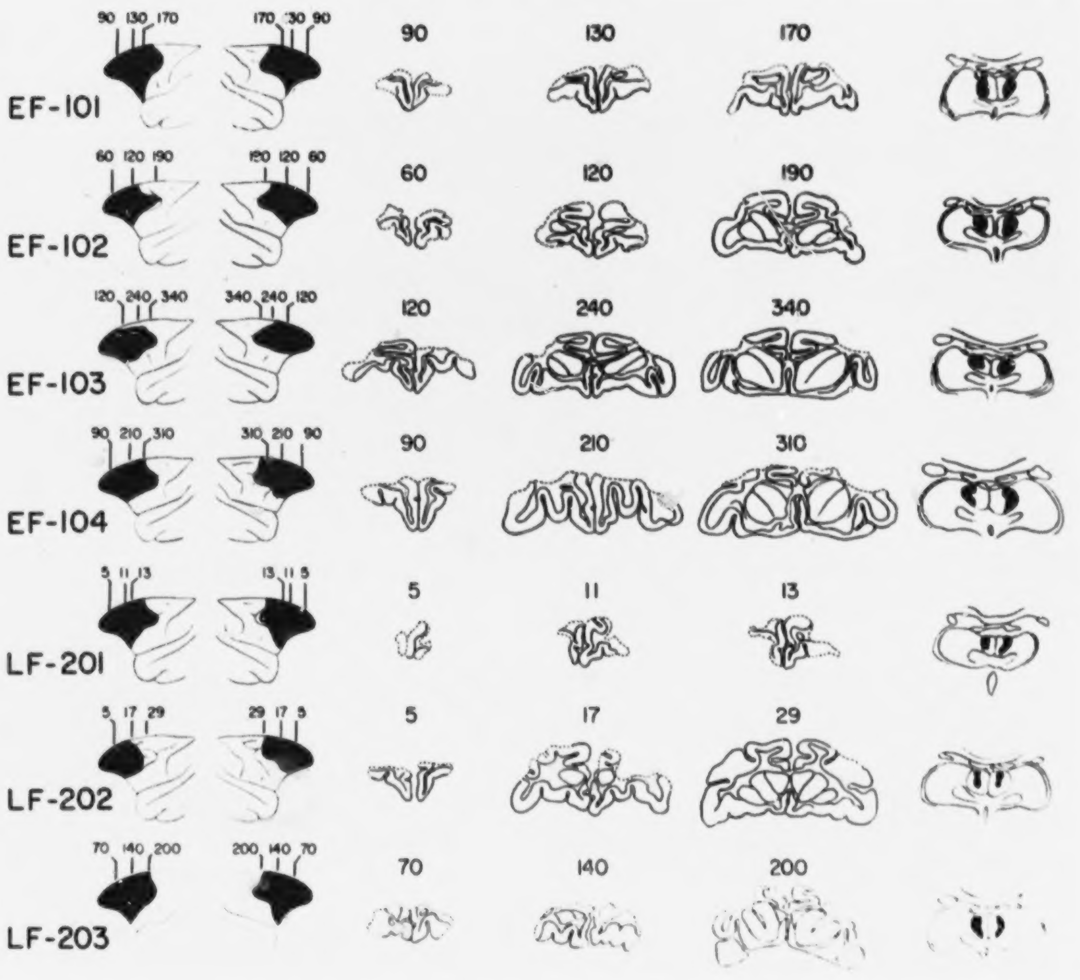

EF-101
90 130 170
170 130 90
90
130
170
EF-102
60 120 190
190 120 60
60
120
190
EF-103
120 240 340
340 240 120
120
240
340
EF-104
90 210 310
310 210 90
90
210
310
LF-201
5 11 13
13 11 5
5
11
13
LF-202
5 17 29
29 17 5
5
17
29
LF-203
70 140 200
200 140 70
70
140
200

FIGURE 1.—Ablation of the frontal granualar cortex in 4 infant (EF 101, 102, 103, 104) and 3 adult monkeys (LF 201, 202, 203).

keys, 3 achieved the 40-second delay interval, and one, the 10-second interval. In one animal there was deterioration of function in that he showed a precipitous drop in delayed response 8 months later.

Having demonstrated that at least up to one year of age ablation of frontal granular cortex in the neonatal period does not impair delayed response performance, a number of other lesions were made in cerebral areas which had been shown to affect this task. Lesions of the caudate nucleus also result in hyperactivity and a definite but less severe disturbance in delayed response.

The other area implicated in disturbances in delayed response is the posterior association cortex. Accordingly, three neonates were subjected to combined lesions of the frontal granular cortex and the head of the caudate nucleus (fig. 2) and three to combined lesions of the frontal granular and posterior association cortex (fig. 3). Adult operates of both types were also prepared and similarly tested. A number of major differences were immediately apparent between those monkeys sustaining combined cortical-subcortical lesions and the cortical lesion alone.

Of a total of seven infants subjected to the frontal caudate lesion, all showed poor sucking and grasping reflexes, poor temperature control, and some degree of

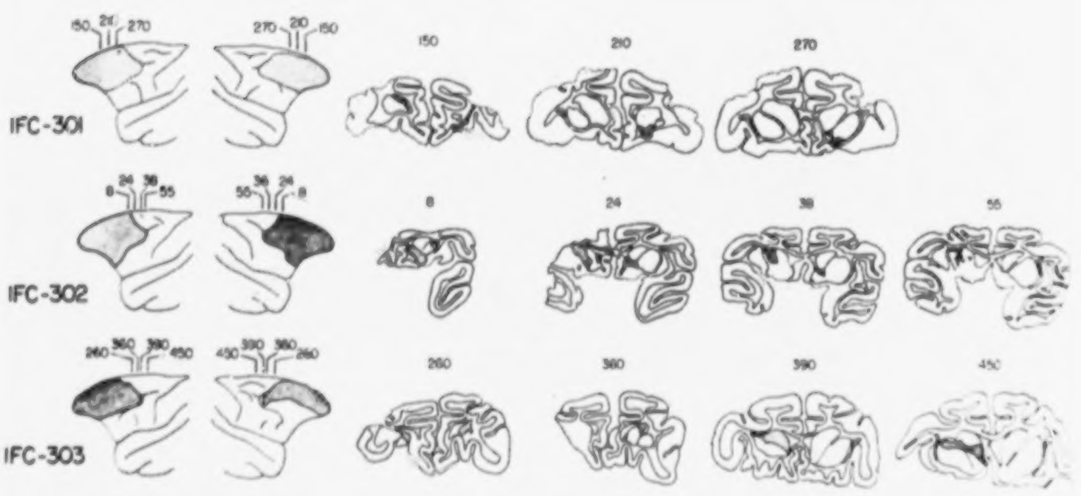

150
210
270
IFC-301
8
24
38
55
IFC-302
260
360
390
450
IFC-303

FIGURE 2.—Combined ablation of the frontal cortex and caudate nucleus in 3 infant monkeys.

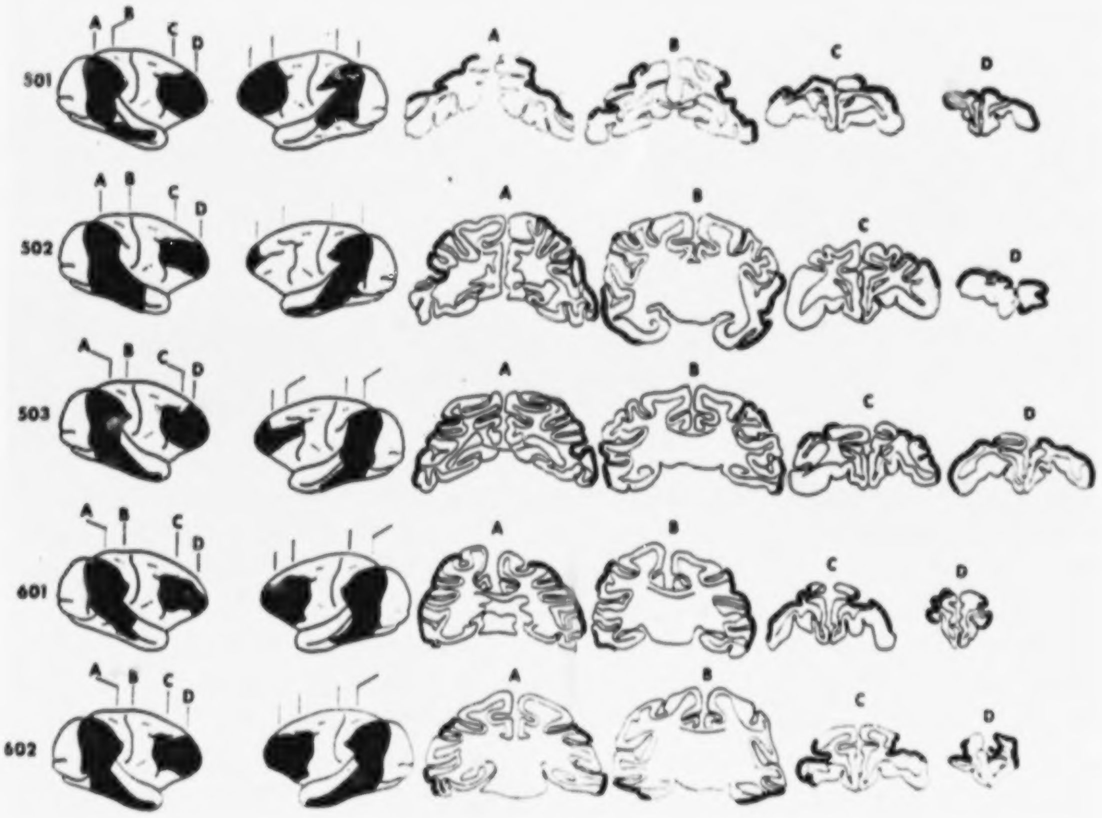

A
B
C
D
501
502
503
601
602

FIGURE 3.—Ablation of the frontal granular cortex and posterior association cortex in 3 infant monkeys (501, 502, 503) and 2 adults (601, 602).

motor paresis. As a result of their deficient sucking and grasping, none could be maternally reared. After being returned to their respective mothers they were frequently found on the floor of the cage, showed gradual inanition, and four subsequently died.

Three subjects were successfully reared in incubators. Two of the 3 had a flaccid paresis of the legs, were hypokinetic, and had very poor sucking reflexes. They vomited frequently, had poor temperature control, and frequent respiratory and gastro-intestinal infections. Their paresis gradually improved and in 2 or 3 months both were walking adequately. As their sucking responses improved, weight gain, which was always below normal, also improved. The third surviving infant who was operated at about 56 days of age, (in contrast to operation on day 2 and day 3) was not as severely affected and at autopsy was found to have sustained only minimal damage to the caudate nucleus.

Another major difference distinguishing those with subcortical lesions was the occurrence of seizures for one week after operation and EEG evidence of episodic seizure activity for at least three postoperative months.

The adult operates recovered uneventfully and displayed the characteristic hyperactivity and circling a day or so after operation. As a consequence of being reared artificially, all infants displayed the maternal deprivation syndrome of withdrawal, hairpulling, exaggerated fear reactions, and excessive nonnutritive sucking. Formal testing for the infant operates began at 7 months of age. The testing behavior of the two with moderate caudate damage was similar to the adult operates in that they were distractable and hyperactive.

The results were that one infant operate with the minimal lesion of caudate nucleus was able to perform delayed response, whereas the other two showed complete failure. Again, none of these animals had any difficulty with color discrimination.

The three infant operates with combined lesion of frontal and posterior association cortex had an uneventful recovery. While they had good sucking and grasping reflexes, they were also reared artificially. Formal testing for this group began at 6 months of age and at 3 months after surgery for two adult operates with similar lesions. In the infant operate group all learned the color discrimination problem and delayed response through 40 seconds, while the adults with this lesion failed to learn the problem.

In addition to the basic test series, the combined frontal posterior group was also tested for object discrimination. This task requires the subject to discriminate two objects differing in size, shape, color, and texture. The adult operates took two or three times the number of trials the infant operates required to master the problem. Since previous study has shown that lesions of posterior association cortex in adults results in marked deficits in tasks, the excellent performance of the infant operates indicates a sparing of this discrimination task in addition to delayed response.

To investigate further the role of isolated areas of neocortex in cognitive function we prepared three monkeys sustaining bilateral neodecortication, sparing only motor and premotor cortex. Each subject was operated in two stages, one week apart. Two of the 3 subjects are now between 2 and 2½ years of age. At the time of this report they have been tested on a variety of tasks. Since they are still alive, we have not verified the extent of their lesions and our conclusions regarding these preparations must be considered tentative.

All infants were operated during their first postnatal month. While they were somewhat weak and hypokinetic for the first postoperative month, sucking and grasping reflexes were excellent. There was no paresis and all developed the maternal deprivation syndrome. Upon observation of their gross behavior in the cage, they were virtually indistinguishable from unoperated, maternally deprived monkeys with the exception of poor distance perception and the tendency to eat directly with their mouths rather than utilizing hand-to-mouth coordination. Physical growth was within normal limits and they looked remarkably healthy in spite of the massive cortical ablation.

Both the subjects mentioned above were first trained in a brightness discrimination which they learned without difficulty. They also learned a pattern discrimination of vertical versus horizontal stripes, but could not learn the circle versus triangle discrimination. Red versus green was learned with great difficulty. On delayed response they did no better than most adult frontal cortex operates which is a 5 second delay period.

It is interesting to note that they were quite hyperactive and distractable in a test situation. While their visual impairment complicates the interpretation of their test performance, they could undoubtedly see well enough to distinguish the test plaques. In the absence of all but motor and premotor cortex these subjects had extraordinary sensory capacities which was evidenced not only by the results of formal testing but by the excessive non-nutritive sucking, fear responses, and obvious tactical sensitivity. This would support the notion that motor cortex has a potential to support considerable sensory function and perhaps more complex behavior as well. A summary of the test results is presented in Table I.

The results of these experiments indicate that the sparing of the ability to perform delayed response after lesions of frontal granular cortex does not rest with the remaining association areas of the cerebral cortex. In fact, limited forms of sensory discrimination and cognitive ability are possible in the absence of most of the cortical mass if the lesion is made early in life. However, this sparing may be sustained only prior to the complete maturation of the neocortex. Damage to subcortical areas in the neonatal period, however, grossly affects cognitive ability as well as those motor and reflex functions necessary for survival. The inability of adult-operated subjects or older infant operates to do better than 5-second delay appears intimately associated with the appearance of hyperactivity and distractability.

Since the caudate damaged animals showed this syndrome much earlier than those with cortical damage alone, it would not seem unreasonable to postulate that at least early in life the caudate nucleus has inhibitory functions which with maturation of the cortex become part of the cortical–subcortical inhibitory system. It would also seem reasonable to suppose that with the maturation of subcortical motor systems, the presence of the inhibitory functions of localized areas of the cortex become increasingly important and not necessarily a function of the mass of cortical tissue removed. This is demonstrated by the superb performance of the infant subjects with combined frontal and posterior cortex lesions.

The ability of the monkey to solve the delayed response problem then is dependent upon sufficient motor inhibition to attend to and hold the information presented. If there is sufficient motor inhibition in even small areas of nonassociation cortex, we may be able to develop sufficient plasticity to enable the animal to solve the problem, if the lesion is made early in life.

It will be recalled that all operated subjects failed delayed alternation no

TABLE. 1—*Summary of formal test results for infant and adult lesioned monkeys*

Groups	Age at Operation (days)	Age at Initial Testing (mos.)	Color Discrimination Trials to Criterion	Delayed response Max. delay (sec.) (Initial Testing)	Delayed Alternation (5 sec.) % correct in 1020 trials
Infant frontals					
IF-101	2	5	150	40	42
IF-102	1	5	60	10	37
IF-103	4	6	60	40	49
IF-104	34	10	60	40	55
Adult frontals					
LF-201	Adult	Adult	90	0	39
LF-202	"	"	60	0	49
LF-203	"	"	120	5	41
Infant frontal caudate					
IFC-301	56	7	65	40	49
IFC-302	15	7	50	Failed	52
IFC-303	2	7	60	0	54
Adult frontal caudate					
LFC-401	Adult	Adult	90	0	52
LFC-402	"	"	189	0	46
LFC-403	"	"	30	Failed	56
Infant frontal post. cortex					
IFP-501	5-15	7	60	40	56
IFP-502	"	7	150	40	90
IFP-503	"	7	90	40	46
Adult frontal post. cortex					
LFP-601	Adult	Adult	60	Failed	46
LFP-602	"	"	60	Failed	48
Infant decortication sparing motor cortex					
Randy	5-30	8-24	1110	5	..
Sean	5-30	8-18	859	5	..

matter at what age they were operated, but they were able to master color discrimination and also object discrimination in the frontal-posterior group. The requirements for the solution of delayed alternation include that the animal develop the concept of go-right, go-left without external sensory cues. It would seem that the frontal cortex is essential for this type of concept-formation and that the effect of the lesion is not age-dependent. However, where the animal can utilize visually-mediated cues such as color or form, considerable plasticity of function would seem to exist. Further, the sparing of sensory function may not deteriorate in time. Experience with lesions of visual cortex indicates that early lesion subjects sustain their initial good performance on visual frequency discrimination well into maturity.

In the monkey, 8 months appears to be critical for the development of hyperactivity, capacity for delayed response, sparing of paresis after motor cortex ablations, as well as the development of spasticity after large cortical lesions in the neonate. By 18 to 24 months the motor and cognitive capacities of the monkey may be reaching maturity and with maturity may require certain localized areas of the cortex.

Further work remains to be done in this area to determine to what extent limited areas of the cerebral cortex can support a number of sensory motor functions and a degree of plasticity. It is also necessary to study these prepararations well into maturity to determine how long the sparing is maintained and at what ages certain functions may show deterioration. In addition, we must perform successive ablations over time of both cortical and subcortical regions to further understand the neural mechanisms observed in this sparing of function.

DISCUSSION

PARTICIPANT: I wonder if we'd see a difference if we made the combined cortical, subcortical lesion in a 2-stage operation. There was a study that Dr. Meyers did some years ago where he trained rats, and then removed some cortex. When he removed it bilaterally, there was almost a 100 percent loss on a retesting of this function. If he did it in a 2-stage way, removing one side, waiting for recovery and then removing the other side, it was almost 100 percent no loss. Interestingly enough, if he did the 2-stage operation, but reared the rats in the dark, there was also a 100 percent loss.

It was a matter of a 2-stage operation, but with normal chance for normal input of light.

DOCTOR KLING: We were talking about this informally last night and I suggested that one of the problems with that experiment was that the animals that were reared in darkness may have had some retinal degeneration, and therefore, it is not fair to look at brain function with a peripheral lesion.

I think it is important to do some serial lesions, but the problem is complicated in this area by the rate of maturation of the brain, so you're dealing with two factors. Since the brain is continuing the process of maturation, you have to be careful about the time sequence of doing these serial ablations. I think though, the monkey offers the best animal, because it is the slowest developing of our experimental animals and would give us plenty of time to do such testing.

DOCTOR DODGE: As clinicians, Dr. Kling, we see children with various types of brain disease in which one of the outward manifestations of disease and/or other factors, is hyperactivity and distractability and are inclined to try drugs in the modification of behavior.

Did you by chance explore the use of amphetamines or other drugs in modifying this particular facet of the behavioral syndrome?

DOCTOR KLING: We did no drug studies on these animals. I think though, now that we have the opportunity with a sufficient number of neonates, that this will be done. Adult operates stay hyperactive but with diminishing intensity. This contrasts with the clinical observations that the hyperactivity syndrome of the human undergoes an age developmental sequence, phasing out in adolesence.

REFERENCES

Kling, A. and Tucker, T.: Sparing of function following localized brain lesions in neonatal monkeys. In: *The Neuropsychology of Development; a Symposium* (ed.) L. Isaacson. John R. Wiley & Sons, *1968.*

Kling, A., Tucker, T. J.: Effects of combined lesions of frontal granular cortex and caudate nucleus in the neonatal monkey. *Brain Res., 6: 428–439* (*Nov*) *1967.*

Tucker, T. J., and Kling, A.: Differential effects of early and late lesions of frontal granular cortex in the monkey. *Brain Res., 5: 377–389* (*July*) *1967.*

SESSION V

The Premature

Session Chairman: SCHUYLER KOHL, M.D., PH.D.

PREMATURE INFANT: INTRACRANIAL HEMORRHAGE AND MENTAL RETARDATION

C. B. Carlson, M.D.
Department of Medicine (Neurology) and Pediatrics
University of Washington School of Medicine
Seattle, Washington

The frequency of the association of intracranial hemorrhage with brain damage and mental retardation is undetermined but potentially of considerable magnitude. The occurrence rate of intracranial hemorrhage has been estimated at 1 percent in all live births (Roberts 1939). However, studies of cerebral spinal fluid in the newborn have demonstrated a 10–20 percent incidence of bloody fluid. Varying estimates of intracranial hemorrhage in newborn infant death range from 9 percent (Haller, et al, 1956) to 33 percent (Srsen 1967). Surveys of survivors of presumed perinatal intracranial hemorrhage show that 10 percent (Craig 1950) to 25 percent (Roberts 1939) show signs of brain damage.

Pathology investigations have demonstrated that the lesions associated with intracranial hemorrhage in the newborn, including the premature, are exclusively venous. Two separate types of hemorrhage are observed—those with subdural location, and those with intracerebral and leptomeningeal location.

The subdural type includes the following lesions:

(1) Rupture of superior cerebral veins with convexity hemorrhage.
(2) Rupture of external surface veins with convexity hemorrhage.
(3) Rupture of the great cerebral vein (Galen) with basilar subtentorial hemorrhage.
(4) Rupture of the tentorium at the straight or transverse sinus with subtentorial or generalized hemorrhage.
(5) Rupture of falx cerebri at tentorial junction with subtentorial hemorrhage.

The intracerebral-leptomeningeal type includes the following:

(1) Hemorrhage from the choroid plexus into the ventricle and subarachnoid space.
(2) Hemorrhage from the terminal veins into the subependymal area.
(3) Isolated pia mater hemorrhage.
(4) Subependymal hemorrhage with rupture into the ventricle and subarachnoid space.

The subdural type occurs mainly in full-term infants and the intracerebral-leptomeningeal type in low-birth-weight, immature infants. (Srsen 1967; Gruenwald 1951).

A great part of the problem in estimating the significance of neonatal intracranial hemorrhage as a cause of brain damage and mental retardation in later life is the difficulty of establishing a diagnosis. Lumbar puncture and analysis of the cerebrospinal fluid is essential to confirm the diagnosis. Craig (1938) has separated the clinical syndromes of subdural, subarachnoid, intraventricular, and intracerebral hemorrhage on the basis of physical and neurologic examination, the appearance of the face, and the state of the fontanelle.

The mechanical basis for the various forms of subdural hemorrhage is well established and will not be discussed. In the premature infant, the more frequent hemorrhage is the intracerebral-leptomeningeal type. The pathogenesis of this is not as well established, although it is generally spoken of as anoxic. Several proposed pathogeneses should be considered, together with evidence of associated disorders.

Factors proposed in the pathogenesis of intracerebral hemorrhage include the following:

(1) Negative intracranial pressure (relative to somatic pressure) leading to venous stasis and hemorrhage (Schwarz 1961).

(2) Anoxia leading to venous congestion and/or vascular damage and venous hemorrhage.

(3) A particular state of the venous-capillary bed in the subependymal regions of the immature brain predisposing it to hemorrhage, due to a variety of stresses (Gruenwald 1951).

(4) Increased venous pressure leading to venous hemorrhage (Schwarz 1961; Schlesinger 1939; Grontoft 1954).

Intracranial hemorrhage is not commonly seen with hemorrhagic disease of the newborn. Recently Gray, et al, (1968) have demonstrated a significant correlation between impaired response with thrombotest on the first day of life and all types of intracerebral hemorrhage in the immature infant, especially the intracerebral form. Hypoglycemia is frequently seen in infants with intracerebral hemorrhage.

REFERENCES

CRAIG, W. S.: Intracranial haemorrhage in the newborn: study of diagnosis and differential diagnosis based upon pathological and clinical findings in 126 cases. *Arch Dis Child 13: 89–124 (June) 1938.*

CRAIG, W. S.: Intracranial irritation in the newborn: Immediate and long term prognosis. *Arch Dis Child* 25:*325–350, (Dec), 1950.*

FLEMING, G. B., and MORTON, E. D.: Meningeal haemorrhage in the new-born. *Arch Dis Child* 5: *361–368, (Oct), 1930.*

GRAY, O. P., ACKERMAN, A., and FRASER, A. J.: Intracranial haemorrhage and clotting defects in low-birth-weight infants. *Lancet* 1:545–548, (March 16) 1968.

GRONTOFT, O.: Intracranial haemorrhage and blood–brain barrier problems in the newborn; a pathologico-anatomical and experimental investigation. *Acta Path Microbiol Scand Suppl 100:1–109, 1954.*

GRUENWALD, P.: Subependymal cerebral hemorrhage in premature infants, and its relation to various injurious influences at birth. *Amer J Obstet Gynec* 61:*1285–1292, (June), 1951.*

HALLER, E. S., NESBITT, R. E., JR., and ANDERSON, G. W.: Clinical and pathologic concepts of gross intracranial hemorrhage in perinatal mortality. *Obstet Gynec Survey 11:179–204 (April), 1956.*

ROBERTS, M. H.: Intracranial hemorrhage in the newborn. *JAMA* 113:*280–284 (July 22), 1939.*

SCHLESINGER, B.: Venous drainage of brain, with special reference to galenic system. *Brain 62: 274–291 (Sept), 1939.*

SCHWARZ, P.: *Birth Injuries of the Newborn;* Morphology, Pathogenesis, Clinical Pathology, and Prevention. New York; Hafner Publishing Co., 1961.

SRSEN, S.: Intraventricular haemorrhage in the newborn and "low birthweight." *Develop Med Child Neurol* 9:*474–480 (Aug), 1967.*

CENTRAL NERVOUS SYSTEM DAMAGE IN THE PREMATURE RELATED TO THE OCCURRENCE OF MENTAL RETARDATION*

Abraham Towbin, M.D.
Danvers State Hospital
Hathorne, Massachusetts
St. Margaret's Hospital
Boston, Massachusetts

The lesions in the brain in mental retardation are the consequence mainly of damage incurred during gestation and birth. Past studies focusing attention on the chronic lesions in the brain in mental retardation—lesions reflecting the end-stage of the process—have yielded limited information regarding pathogenesis. Patently, the key to the pathogenesis lies in the study of related antecendent lesions. In the studies presented here, patterns of cerebral damage in mental retardation and cerebral palsy are correlated with patterns of cerebral damage that make their appearance during gestation and birth.

In this study, reflecting the experience of the present investigator over the past 17 years, a broad source of both acute (fetal and neonatal) and chronic case material (mental retardation, cerebral palsy, and epilepsy) was available. The pathology studies of the patterns of chronic cerebral damage were carried out at Columbus State School, Columbus, Ohio from 1951 to 1955 and at the Deutsche Forschungsanstalt für Psychiatrie, Max-Planck-Institut, Munich, 1957–1958. Attention was then directed to the study of acute neonatal case material carried out in association with the National Collaborative Perinatal Project, 1962–1965.

Four basic concepts bearing upon the pathogenesis of organic mental retardation emerged from these investigations:

(1) The brain damage is incurred mainly in the prenatal period. The widely held notion that mental retardation and cerebral palsy are conditions due to "birth injury" is in large measure a misconception. Evidence indicates that in most instances the damage is of hypoxic origin and, in many cases, is imprinted in the fetal brain prior to labor, often weeks or months before delivery.

(2) Systemic processes are responsible for the neonatal cerebral damage leading to mental retardation. The cerebral lesions in the fetus and neonate are not due to local processes, such as trauma or kinking of the vena galen, but result from systemic disorders involving maternal, placental, fetal, or neonatal mechanisms.

---

*Photographs by Mr. Leo Goodman, Boston, Mass.

(3) The cerebral lesions are formed through the process of venous infarction. Interpretation of the lesions as hemorrhage, necrosis, or anoxia is pathologically inconclusive.

(4) The occurrence of cases with subacute cerebral damage provides a transitional pathologic link between the acute neonatal and chronic cerebral lesions.

In the neuropathology laboratory, the study of the neonatal brain—soft, friable, and often diffluent—has been complicated by technical difficulties. Traditionally, the examination of the newborn brain using routine histologic sections was held to yield little information. The case material in the Warren Anatomical Museum, Harvard University Medical School, prepared in conjunction with the National Collaborative Perinatal Project, was used in this study. The technique of whole-brain serial histologic sectioning made possible the preservation of focal lesions and the consistent demonstration of their geographic relationships in the brain. Over 600 clinically correlated brain specimens, a major portion in the premature age group, were studied. The pathology studies indicated that the cerebral lesions in the fetus and newborn were due essentially to two primary pathologic processes: mechanical trauma and hypoxia. From these processes, four main forms of central nervous system damage are derived (Table 1): subdural hemorrhage from dural-venous laceration; spinal cord and brain stem injury (at birth); deep cerebral venous infarction (in the premature); cortical cerebral venous infarction (at term).

TABLE 1.—*Neonatal central nervous system damage*

	4 Main Forms
	....
	Mechanical Trauma
I.	Subdural hemorrhage from dural-venous laceration
II.	Spinal cord and brain stem injury
	....
	Hypoxic Damage
III.	Deep cerebral venous infarction (in the premature)
IV.	Cortical cerebral venous infarction (at term)

A host of other pathologic processes affecting the nervous system—genetic anomalies, infectious diseases, and metabolic defects—although manifestly rare and contributing only a small portion of cases of mental retardation, consume vast academic attention. In a broad perspective, hypoxic cerebral damage—particularly periventricular cerebral infarction in the premature—makes up the bulk of case material related to organic mental retardation and cerebral palsy.

Acute Forms of Central Nervous System Damage

Subdural hemorrhage from dural-venous laceration. Of the basic pathologic processes affecting the central nervous system in the newborn, subdural hemorrhage is the most familiar to patthologists and clinicians (Table 2). It is the one form of intracranial damage that at times is amenable to surgical treatment. Two main patterns occur. The cerebral (supratentorial) form, with blood distributed over the cerebral convexity, occurs mainly in term infants and is usually

TABLE 2.—*Neonatal subdural hemorrhage due to dural-venous laceration*

Lesion	Occurrence	Causal Factors	Subdural Hemorrhage Localization	Effects
Tentorium; Junction of tentorium and falx	More common in term than in premature	Vertex presentation with excessive vertical molding and with forceps application in A–P diameter. In face and brow presentation producing anteroposterior elongation of head.	Basal cerebral hemorrhage with "incomplete" tentorial tears. Into posterior fossa with extension of tears to dural sinus or vena galen.	Supratentorial tears usually tolerated. Posterior fossa tears rapidly fatal.
Falx tears	Rare	Face and brow presentation producing antero-posterior elongation.	In longitudinal cerebral fissure, over the corpus callosum.	Usually incidental finding at autopsy.
Vena galen tear	Term and premature	With vertical and anteroposterior elongation.	Commonly posterior fossa, also combined with basal cerebral hemorrhage.	Posterior fossa hemorrhage produces rapid lethal compression of brain stem.
Circumferential dural sinuses		With fractures; occipital bone diastasis with laceration of lateral sinus. Overriding of parietal bones with laceration of superior sagittal sinus.	Hemorrhage in region of sinus laceration or fracture.	Rapid accumulation of blood; precipitous death with lateral vein laceration, with posterior fossa hemorrhage.
Superior superficial cerebral veins (bridging veins)	Common at term	All forms of cephalic molding, especially vertical; stretch-tears of bridging veins, overlaping of interparietal fissure.	Usually thinly spread over the superior surface of cerebrum (subarachnoid bleeding often also occurs) Localized hematoma, frontoparietal, at times.	Usually well tolerated when dispersed over the hemisphere. Cerebral compression with localized hematoma.

0281

of minor degree. Cerebral subdural hemorrhage of extensive degree, although frequently suspected clinically, is uncommon and is extremely rare in the premature. Subtentorial subdural hemorrhage, with posterior fossa accumulation of blood, leads to compression of the brain stem, to suppression of vital function, and, usually, to rapid death. Subtentorial hemorrhage occurs commonly both in premature infants and at term.

Subdural hemorrhage occurs in association with cranial molding during delivery. Elongation of the head during molding is the consequence of forces of lateral compression exerted on the fetus in the descent through the birth canal. Although commonly viewed as a physiologic part of the process of parturition, molding may lead to intolerable strain on the taut intracranial dural sheets, the tentorium and falx. Excessive stretch leads to their laceration; when the laceration extends to the venous sinsues within the dural sheets, bleeding into the subdural space occurs. The most frequent site of damage is at the junction of the falx and tentorium, near the attachment of the vena galen (fig. 1). At times the bleeding is due to laceration of the vena galen. Injury to these structures, occurring with vertical molding of the head in vertex presentation, commonly leads to fatal posterior fossa hemorrhage.

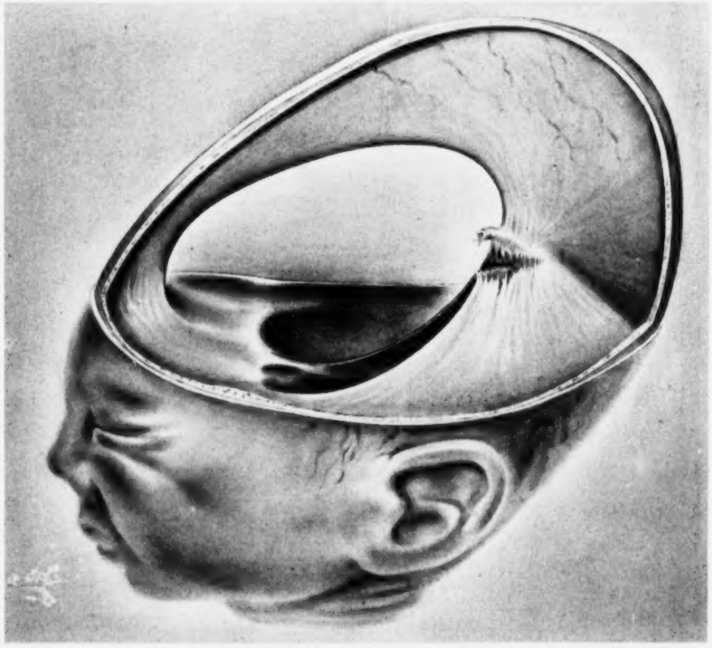


FIGURE 1—Dural-venous laceration at the junction of the falx cerebri and tentorium cerebelli, near the attachment of the vena galen and the straight sinus, consequent to vertical molding distortion of the head; laceration of the straight sinus commonly leads to posterior fossa hemorrhage.

Similarly, molding distortion of the head with stretching and laceration of the bridging veins between the superior aspect of the cerebrum and the superior sagittal sinus leads to cerebral convexity subdural hemorrhage. Since the superficial cerebral veins become developed relatively late in fetal life, cerebral subdural hemorrhage in the premature is rare.

Essentially, subdural hemorrhage in the neonate exerts an all-or-none effect, depending on its location. When the bleeding occurs over the cerebral convexity, usually in a thinly dispersed sheet (commonly an incidental finding at autopsy in the term newborn), it is symptomless. When the bleeding occurs in the posterior fossa, it is usually rapidly fatal. Accordingly, while subdural hemorrhage is important in neonatal mortality, it is of limited significance in the pathogenesis of mental retardation, cerebral palsy, and other pediatric neuorologic sequelae.

Spinal cord and brain stem injury. Most of the signs of neonatal injury observed in the delivery room reflect the presence or absence of damage to the brain stem and spinal cord. The initiation of respiration, sustained cardiac function, muscle tone, irritability, and other elementary signs related to the Apgar score depend on the intact function of the brain stem and cord.

Spinal cord and brain stem injuries occur commonly at birth. Past autopsy investigations in which the spinal structures were studied in detail indicate the presence of spinal injury in 10 to 33 percent of newborn deaths (Litzmann; Stoltzenberg; Pierson; Toverud; Hausbrandt; Zellweger; Volbert and Schweitzer; Yates; Coutelle).

The importance of this form of parturitional injury has failed to gain sustained attention, however, being overshadowed first by the problem of subdural hemorrhage and lately by concern with hypoxic damage to the cerebrum. Cases of frank fracture of the spine with mangling transection of the cord—the result of obstetrical trauma—still occur. While these obvious forms of spinal injury are recognized, less severe anatomic damage generally escapes diagnosis clinically and pathologically. In most institutions, examination of the spinal canal is not included as a routine part of the neonatal autopsy.

The common patterns of traumatic damage are indicated in Table 3. Detailed studies with serial histologic sections of the cord and brain stem reveal a broad range of nontransectional lesions, associated with varying damage to neighboring structures (Towbin, 1964).

Epidural hemorrhage is the most frequent manifestation of spinal damage in the newborn (fig. 2) and is seen in the very early premature as well, most commonly affecting the cervical segment. In itself, spinal epidural hemorrhage in the neonate is not a killing lesion; however, its presence indicates spinal injury. The force of the injury may impair cervical cord function, bringing about spinal shock and suppression of respiration and other vital function. Varying anatomical damage to the cord, brain stem, nerve rootlets, and meninges may accompany epidural spinal hemorrhage (fig. 3).

Brain stem damage appears in two main patterns. Stretch injury results in laceration of cerebellar peduncles and deep injury to structures of the mid- and lower brain stem, accompanied by local hemorrhage. Pressure injury is due to herniation of the brain stem, with resulting surface laceration of the cerebellum and consequent posterior fossa hemorrhage (fig. 4).

Spinal cord and brain stem damage may occur during intrauterine life, as a result of fetal malposition; during labor, as the fetus is compressed and pistoned down the birth canal; or during the final extraction of the half-delivered fetus. During delivery, excessive longitudinal traction with flexion, hyperextension, or torsion of the spinal axis is thought to be the most important cause of neonatal spinal and brain stem injury. Such injury may occur with traction on the trunk to obtain the aftercoming head in breech delivery or with forceps traction in ce-

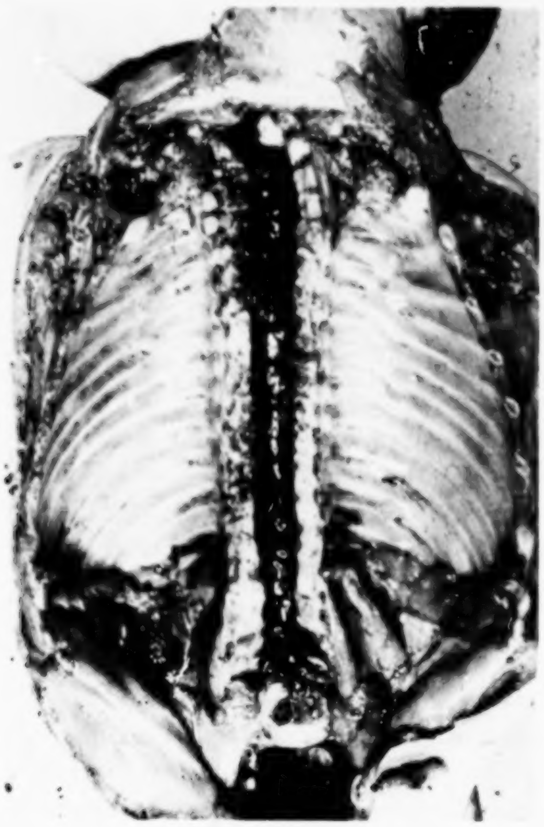


FIGURE 2—Premature infant; spinal epidural hemorrhage; seven months' gestation. Respiratory depression present after delivery. Lived 36 hours. (GMH A-5-62).

phalic delivery. The premature fetus, who is forced through a rigid cervical opening, a physiologically unprepared, unrelaxed birth canal, readily incurs spinal and brain stem injury. Primiparity and precipitous delivery also contributing to the occurrence of such injury.

In cervical spinal injury, Yates has pointed out lessions of the vertebral arteries which might lead to interference with regional blood supply and local ischemic damage in the brain stem. Most observers believe that neonatal spinal and brain stem lesions—varying from frank spinal fracture to minor anatomical disturbances—are of immediate effect and are due to direct mechanical trauma.

In the present study, evidence of significant spinal or brain stem injury was present in over 10 percent of cases; this coincides with past investigations. Spinal injury is estimated to cause 10,000–20,000 neonatal deaths yearly in the United States.

The ultimate effects of such damage are manifested in four different clinical patterns, reflecting the severity of the injury and the survival time. In one group, death occurs rapidly, during labor or directly after birth; it is the consequence of intolerable injury to vital regulatory centers in the brain stem and upper cord. In the second group, death occurs after a short period; central respiratory depression, punctuated by periods of apnea, is complicated ultimately by superimposed peripheral pulmonary complications, the development of pneumo-

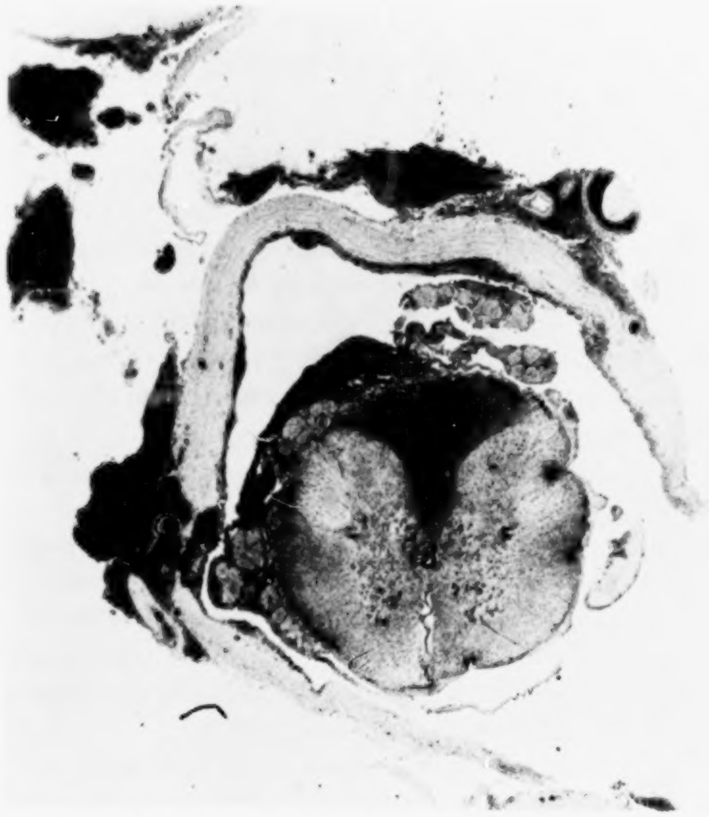


Figure 3—Spinal cord injury; epidural hemorrhage; dural laceration. Premature infant, 37 weeks' gestation. Hypotonia; respiratory depression at birth. Died 16 hours after delivery. (W–107: WAM).

nia, or hyaline membrane disease. Neurologically, the picture of prolonged spinal shock is associated with limpness and collapse of visceral function.

In the third group—infants with injury of the spinal cord or brain stem manifest at birth—the effects may be transient, or the paralyzed infants may sur-

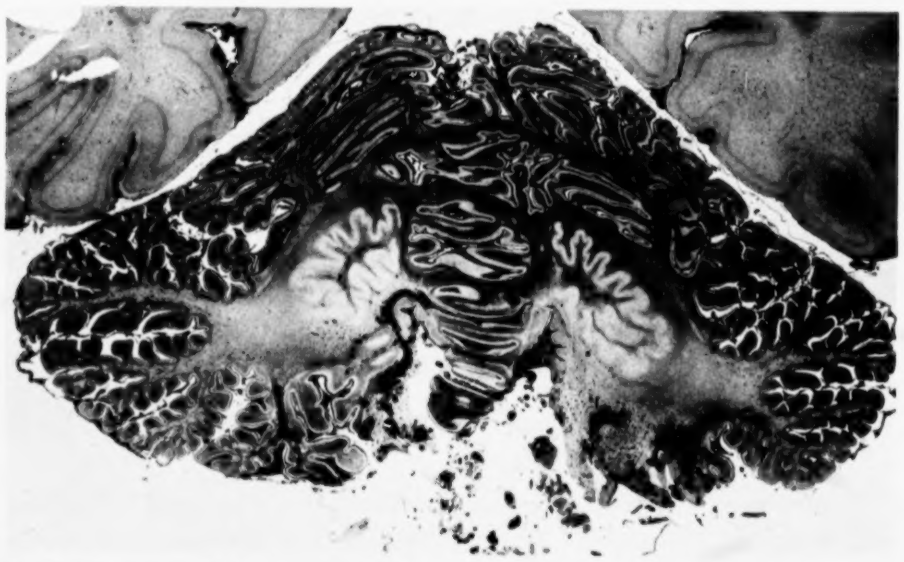


Figure 4—Brain stem injury; cerebellar cortical laceration due to foramen magnum herniation. Complicated forceps delivery. (W–55 WAM).

vive for months or years. Clinically, there may exist a large group of cases with latent sequelae of spinal injury incurred at birth who do not attract clinical attention—children who appear awkward or are spastic and are relegated to the group of cerebral palsy.

The fourth group is made up of infants who survive neonatal spinal injury and who may manifest secondary nuerologic deficits due to hypoxic damage to the cerebrum. Respiratory depression and systemic hypoxia imposed at birth by spinal and brain stem injury in some instances evoke cerebral periventricular infarctional damage in the premature, and in the term infant may result in cortical infarctional damage. Neonatal cerebral damage thus incurred may ultimately be responsible for the blighting of mentation, the motor deficits of cerebral palsy, or the development of epilepsy.

Deep cerebral venous infarction in the premature. This was the most frequent process of damage in this study. In the fetus and premature newborn, the destruction of periventricular tissue is commonly followed by massive intraventricular hemorrhage. Extension of the bleeding from the ventricular system into the subarachnoid space of the posterior fossa, leading to rapid death, occurs commonly. This syndrome, its cause long an enigma, is encountered mainly at the gestational age of 22 to 35 weeks. This process is said to contribute to over 10 percent of neonatal deaths (Arey and Anderson, 1965).

Previous studies have shown that the deep cerebral damage and accompanying intraventricular hemorrhage are not of traumatic nature or arterial origin, as sometimes thought, but are the result of venous hemorrhagic infarction.

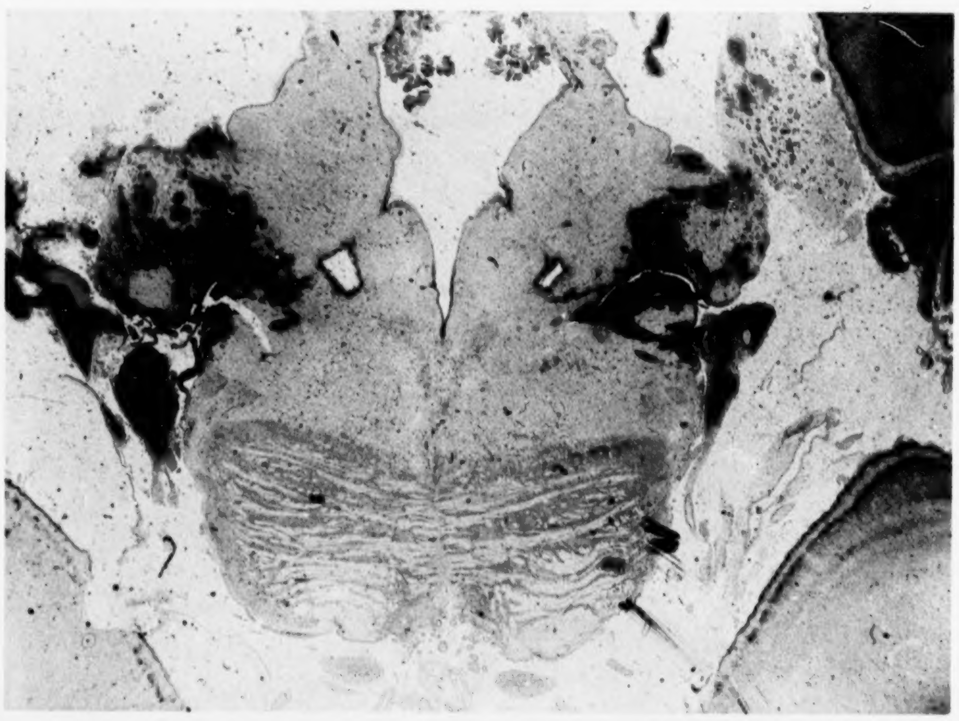


FIGURE 5—Brain stem damage due to stretch-injury incurred at birth; laceration and hemorrhage involving the cerebellar peduncles and other structures about the fourth ventricle. Complicated breech extraction; infant hypotonic, cyanotic, with depressed respirations at birth; death after 2½ hours. Autopsy also revealed a fracture of the thoracic spine. (W-39 WAM).

TABLE 3.—*Spinal cord and brain stem injury at birth*

Patterns of Damage
Cord Lesions
Laceration
Neuronal damage, acute
Edema and congestion
Focal malacia, hemorrhage
Brain Stem Lesions
Laceration (stretch-tears)
Cerebellar cortical laceration (pressure erosion)
Local hemorrhage
Spinal (Cranial) Nerve Root Lesions
Tears, avulsion
Perineural hemorrhage
Meningeal Lesions
Dural tears
Dural hemorrhage (epi-, sub-, and intramural)
Arachnoidal congestion; subarachnoidal hemorrhage

Hemorrhage, the most common manifestation of neonatal central nervous system damage, is not a clinical or pathological entity. The term has comprehensive meaning only when consideration is given to its underlying cause. In neonatology, a fixed concept vaguely attributes hemorrhagic lesions of the brain and meninges to "anoxia." The primary mechanisms causing hemorrhage in the central nervous system of the fetus and neonate, as defined in the present investigation, are indicated in Table 4. Fundamentally, hemorrhage may be of venous or arterial origin and commonly is due to intravascular hypertension, coagulation defects, or breakdown of vessel walls, as occurs in infarction.

The underlying pathologic mechanisms in hemorrhage and infarction are closely linked. Infarctional damage generally results from interference with local blood circulation due to suppression of either arterial inflow or venous outflow. The latter mechanism, infarction due to venous stasis, often escapes consideration. In the fetal-neonatal age group, as in the adult, venous infarction occurs most often in organs with great circulatory inflow and outflow, commonly the brain and kidney. The process of infarction develops gradually, with suppression of circulation being complete or incomplete, with or without thrombosis.

Venous infarction in the brain as in other organs frequently first manifests its presence as hemorrhage, focal or massive. This damages not only the parenchymal cells but also the stromal elements, particularly the veins. In affected areas, with the breakdown of engorged necrotic veins, petechiae appear; ultimately the disintegrating tissue may become flooded with blood.

In the premature, the deep venous system is primarily involved in the development of cerebral infarction and hemorrhage. With circulatory stasis in the vena galen exerting its effect retrograde, the process of venous congestion and thrombosis manifests itself in the deep tributary veins, and the related periventricular cerebral tissue undergoes hemorrhagic infarction (fig. 6).

The location of the cerebral infarctional lesions in the deep periventricular structures is not an incidental occurrence, but is influenced by three specific biologic factors.

TABLE 4.—*Intracranial hemorrhage in the newborn*

Type	Occurrence	Cause	Pathogenesis	Patterns	Pathologic Significance	Clinical Effects
1. Subdural Hemorrhage	Supratentorial in term infants mainly. Subtentorial in premature and term	Trauma	Molding and other forceful cranial distortion: tearing of dural-venous structures	Supratentorial bleeding most common; subtentorial (posterior fossa)	Supratentorial form usually latent; posterior fossa hemorrhage leads to brain stem compression	Supratentorial form usually tolerated subtentorial form usually rapidly fatal
2. (Spinal cord) Brain stem Hemorrhage	Premature and term	Trauma	Excessive traction, torsion, and flexion during delivery leads to stretch injury and pressure injury in the upper cord and brain stem	Spinal epidural hemorrhage most common lesion observed grossly. Posterior fossa hemorrhage consequent to brain stem laceration	Spinal epidural hemorrhage indicates trauma to local structures. Traction leads to cerebellar herniation erosion and deep brain stem laceration	Hemorrhage usually of secondary importance. Mortality and morbidity due to associated injury to vital centers
3. Intraventricular hemorrhage due to periventricular venous infarcts	Premature infants, almost exclusively	Hypoxia; placental defects; intrauterine hypoxia	Fetal-neonatal hypoxic circulatory failure; deep cerebral venous stasis; infarction of subependymal germinal matrix	Bleeding varies from slight oozing to massive intraventricular hemorrhage with extension to subarachnoid space of posterior fossa	Mild forms remain latent; massive hemorrhage extends to posterior fossa; compression of vital medullary structures	Mild forms tolerated; massive hemorrhage precipitates death
4. Cortical venous infarcts with subarachnoid hemorrhage	Term	Hypoxia; placental disorders	Fetal-neonatal hypoxic circulatory failure; systemic venous statis; superficial cerebral veins involved	Cortical laminar necrosis and hemorrhagic infarcts, secondary subarachnoid hemorrhage	Lesions localized or diffuse; usually not lethal	Cortical damage tolerated neonatally; chronic neurologic deficits in surviving infants

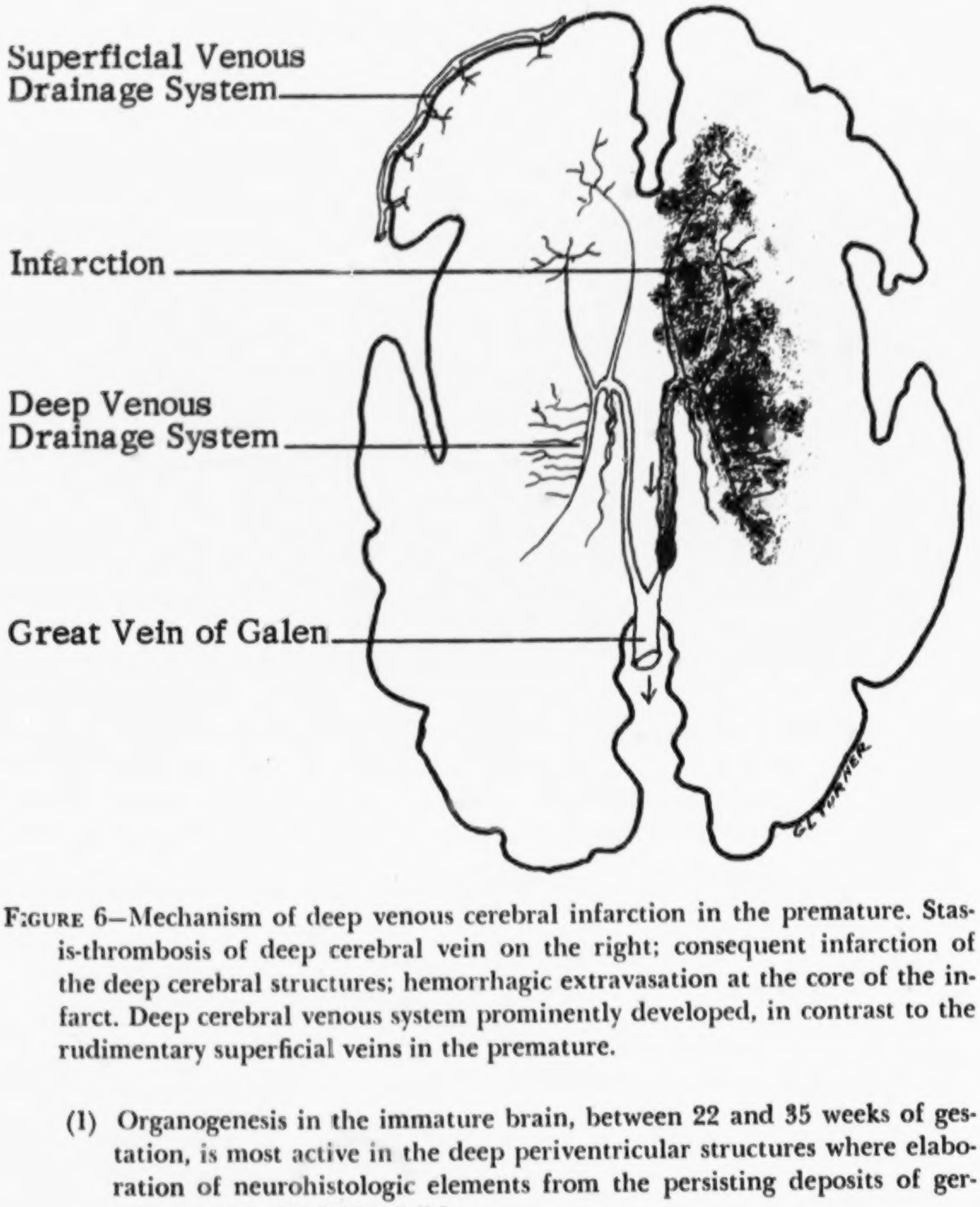

Superficial Venous Drainage System
Infarction
Deep Venous Drainage System
Great Vein of Galen

FIGURE 6—Mechanism of deep venous cerebral infarction in the premature. Stasis-thrombosis of deep cerebral vein on the right; consequent infarction of the deep cerebral structures; hemorrhagic extravasation at the core of the infarct. Deep cerebral venous system prominently developed, in contrast to the rudimentary superficial veins in the premature.

(1) Organogenesis in the immature brain, between 22 and 35 weeks of gestation, is most active in the deep periventricular structures where elaboration of neurohistologic elements from the persisting deposits of germinal matrix is highly visible.
(2) Germinal matrix tissue persists in the cerebrum of the early fetus and premature newborn, forming thick subependymal accumulations protruding into the lateral ventricles (fig. 7). The cerebral matrix, analogous to the inner layer of germinal cells in the primitive neural tube, is a depot of spongioblastic anlage tissue required in the future formation of the cerebral cortex and deep neuronal assemblies. These masses of subependymal germinal tissue, highly cellular and richly vascularized, are manifestly vulnerable to hypoxia, readily undergoing disintegration. In the fetus and neonate, as the gestational age advances, the matrix deposits become smaller; correspondingly, the occurrence of neonatal deep cerebral hypoxic lesions become less frequent and less extensive.

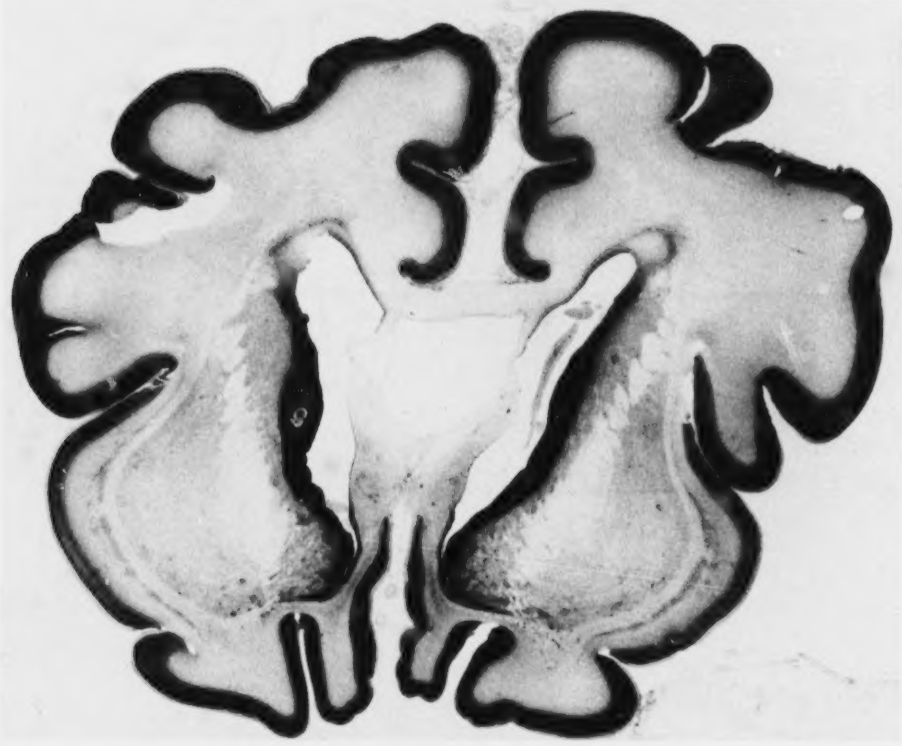


Figure 7—Germinal matrix tissue in the premature human fetal brain (gestational age, 32 weeks); thick, compact, deeply staining periventricular (subependymal) germinal matrix layer on the lateral walls of the cerebrum; on the left, dilatation and thrombosis of the vena terminalis, with perivascular hemorrhagic patch of matrix devastation. (T–3).

(3) The deep venous drainage system in the premature is prominently formed, the superficial cerebral veins being still undeveloped and inconspicuous. In the deep cerebral tissue of the premature fetus and newborn, not only are the parenchymal elements being actively proliferated but also the vascular structures, especially the veins. In the early fetal and premature newborn brain, seen in whole-brain histologic sections, the veins of the Galen system stand out strikingly; stasis in the vena galen is directly reflected upstream, the cerebral periventricular zones becoming engorged (fig. 8). With mounting circulatory congestion, the veins in the subependymal matrix tissue undergo great dilatation, forming venous lakes (fig. 9). As the process of local venous stasis and thrombosis becomes more manifest, the adjoining matrix tissue undergoes necrosis, ultimately showing advanced hemorrhagic infarction (fig. 10). Diffuse destruction of the deep cerebral tissue may follow as the process of infarction extends outward from the matrix, overrunning the periventricular structures (fig. 11).

The process of infarction may ultimately extend deeply into the cerebral wall (fig. 12). Serial whole-brain histologic sections demonstrate thrombosis of the vena terminalis near the foramen of Monroe. The entire thickness of the cerebral hemispheric wall is rendered necrotic on one side; the tide of hemorrhage,

22055

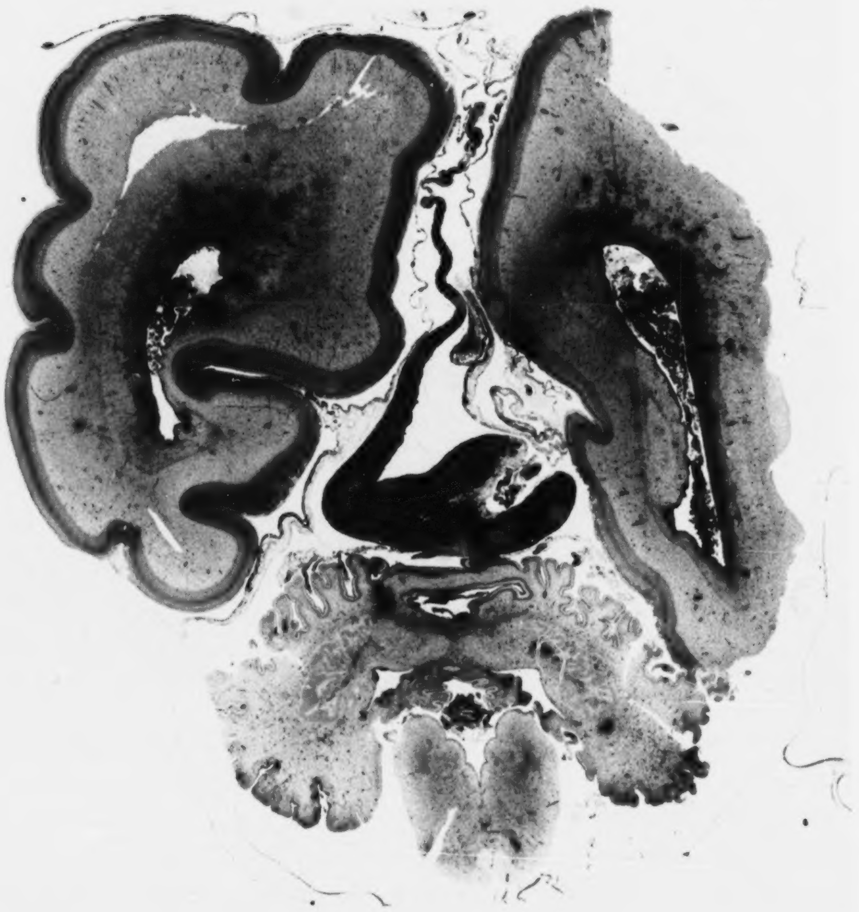


FIGURE 8—Galen vein dilatation and thrombosis. The vena galen and tributaries are black-staining and extend medially in a tortuous expanding course. Retrograde thrust of the venous engorgement is evident in the periventricular tributaries; dilated veins, petechiae, and confluent areas of hemorrhagic necrosis present. Premature infant of 29 weeks' gestation; lived 30 hours. Abruptio placentae. Hyaline membrane disease. Frontal-horizontal section of brain. Loyez stain. (W–12 WAM).

however, extends only through the deep periventricular tissues, where the veins of the deep drainage system are prominently developed at this age of gestation. The outer layers of the cerebrum, still poorly vascularized, are necrotic but not hemorrhagic.

Small areas of necrosis, termed periventricular leucomalacia, at times make their appearance in the deep white matter of the cerebrum in the premature; such focal lesions, having the character of microinfarcts, may form in a satellite pattern about the margin of large venous infarcts or may occur independently in the bed of the deep cerebral venous drainage system.

Cerebral venous infarction in the fetus and newborn is not a local phenomenon, but represents the end-stage in a consecutive series of systemic processes stemming from hypoxia-producing disturbances in the maternal-placental-fetal-neonatal organization. In analyzing the pathogenesis of hypoxic cerebral damage

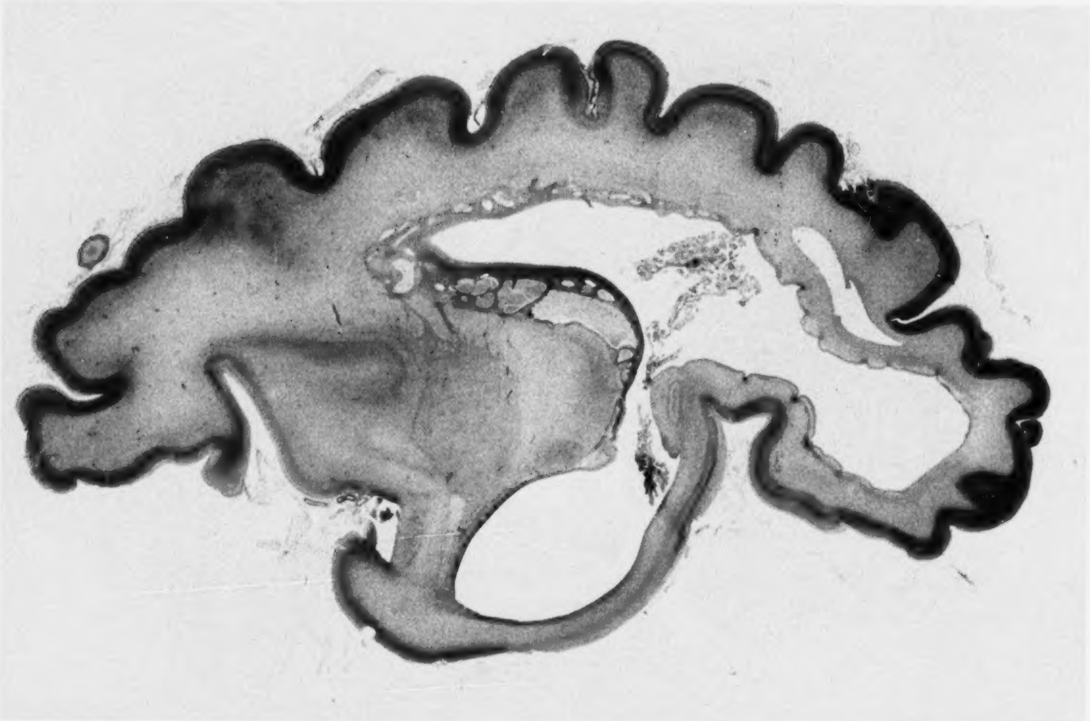


FIGURE 9—Dilatation and congestion of veins in the subependymal germinal matrix tissue in cerebrum of premature infant (29 weeks' gestation). The venous structures, tributaries of the vena galen, appear as broad lakes filled with conglutinated blood. Infant lived 2 hours; autopsy showed evidence of congestive heart failure with cyanosis, ascites, and acute congestion of the liver, spleen, brain, and other viscera. Parasagittal section of the brain. (B–20 WAM).

in the newborn, it is necessary to focus on the course of events occurring systemically and locally. The neuropathologic processes cannot be interpreted comprehensively without taking into account the obstetrical history, the neonatal course, the pathologic findings in the placenta, and the findings in the general autopsy. Viewed thus, a basic pattern of pathogenesis emerges. Gestational complications with consequent fetal-neonatal hypoxia are associated with mounting impairment of vital function, progressive circulatory failure, and generalized bodily venous congestion; local venous stasis-thrombosis results in visceral (cerebral) infarction, often hemorrhagic.

Accordingly, the pathogenesis of neonatal hypoxic infarctional lesions in the cerebrum evolves through three consecutive stages, each precipitating the next:

(1) The hypoxia-producing complication may begin before, during, or after parturition. Hypoxia having onset in utero may extend postnatally, particularly in the premature. In the present study, episodes of maternal illness, toxemia, infection, and anemia were frequently recorded in the last trimester. Vaginal bleeding prenatally was common. The gestational complication causing fetal hypoxia frequently proved to be of placental origin, often premature detachment or placenta previa. The placental defect, umbilical cord compression, or other hypoxia-produc-

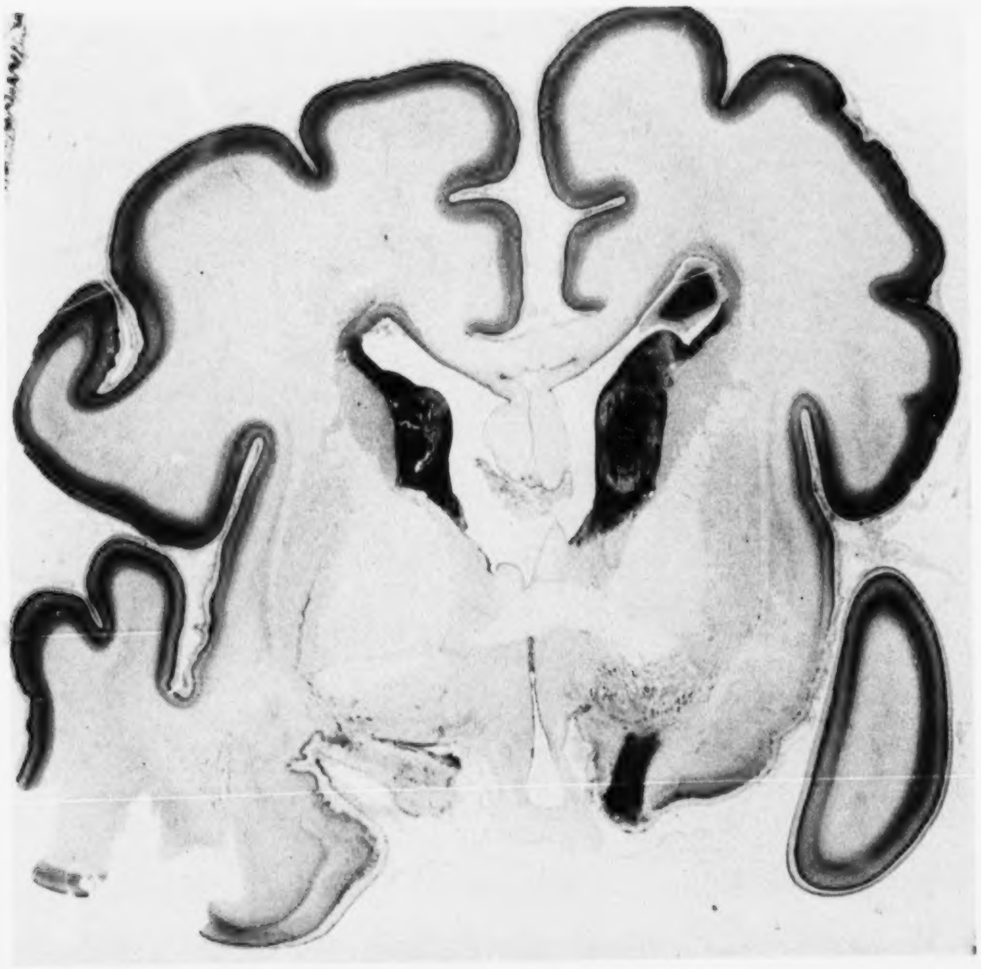


FIGURE 10—Hemorrhagic venous infarction of subependymal matrix; dilation of small and large matrix veins with stasis-thrombosis of blood. Early lesion on the left showing small focal area of hemorrhagic necrosis in the matrix. More extensive lesion on the right giving rise to intraventricular hemorrhage. Premature infant, 27 weeks' gestation; lived 45 hours. Abruptio placentae. Autopsy also revealed multiple thromboses in the mesenteric and portal veins with early infarction of the intestine; pulmonary embolism. (W-73 WAM).

ing mechanisms in utero may precipitate death of the fetus or neonate soon after delivery.

Broad autopsy evidence indicates that intrauterine hypoxia in the period prior to delivery may lead to destructive changes in the fetal brain. (Towbin, 1965; Manterola et al; Toverud; MacGregor, 1946; Cruickshank, 1930). The findings in the lungs in cases of cerebral intraventricular hemorrhage are of particular interest; histologically, the lungs often show frank evidence of amniotic fluid aspiration, the consequence of hypoxia-stimulated attempts at respiration in utero. These findings, observed even in prematures who live for a period, indicate the early (intrauterine) time of onset of the hypoxic process in these cases. Confirmation of the intrauterine development of deep cerebral infarctional

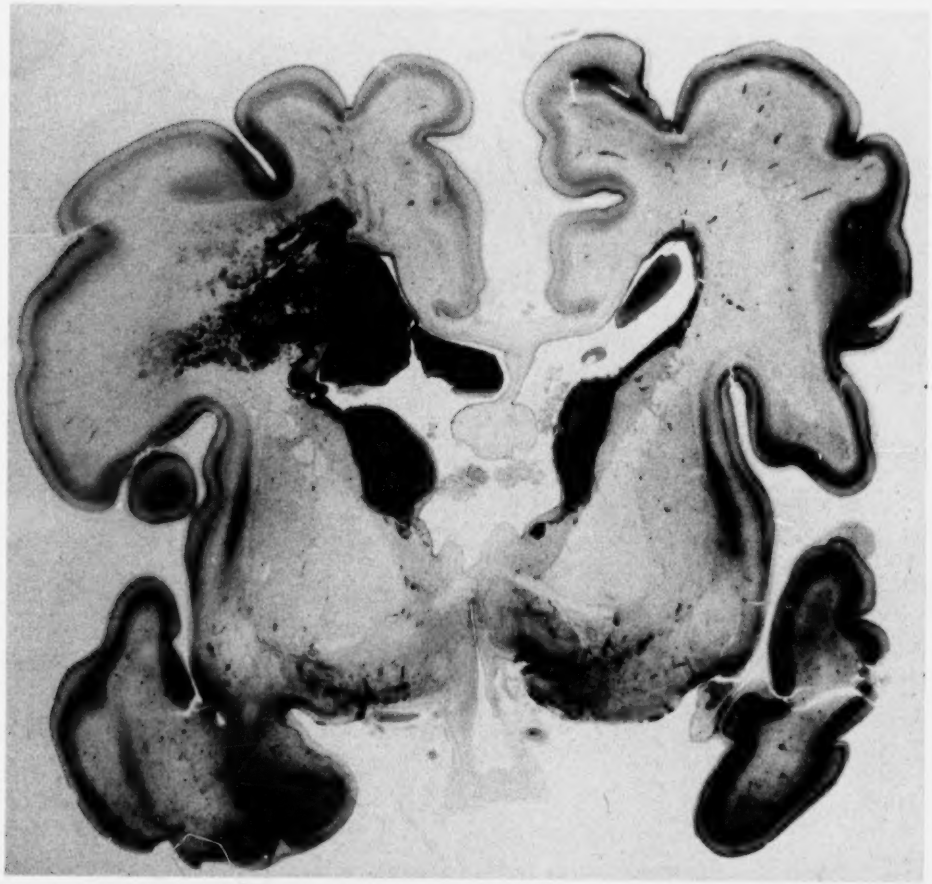


FIGURE 11—Infarction of cerebral subependymal matrix and periventricular white matter; hemorrhagic suffusion into infarcted cerebral substance; thrombosis of periventricular veins; intraventricular hemorrhage. Premature infant, 35 weeks' gestation; lived 23 hours. (W–59 WAM).

damage is evident in cases of slightly macerated fetuses presenting typical intraventricular hemorrhage, and in MacGregor's study—periventricular hemorrhage was present in 19 stillborn infants in 156 cases of intraventricular hemorrhage.

The effects of gestational and parturitional hypoxic complications are plainly visible in the delivery room; the infant is cyanotic and limp and has an Apgar score of 1 to 4. In the premature, peripheral respiratory complications develop commonly, compounding the damaging effects of hypoxia.

(2) Systemic circulatory failure develops consistently in the body as the result of hypoxia sustained over a prolonged period. In the fetus and newborn, deterioration of cardiovascular function becomes manifest, with generalized systemic venous congestion. Measured clinically, venous pressure rises. As emphasized by Cruickshank, Clifford, Potter, MacGregor and others, necropsy regularly reveals findings reflecting systemic congestive failure—cyanosis, peripheral edema, ascites, cardiac dilatation, and enlargement and engorgement of the liver, spleen and other viscera; the brain characteristically is swollen and congested. General-

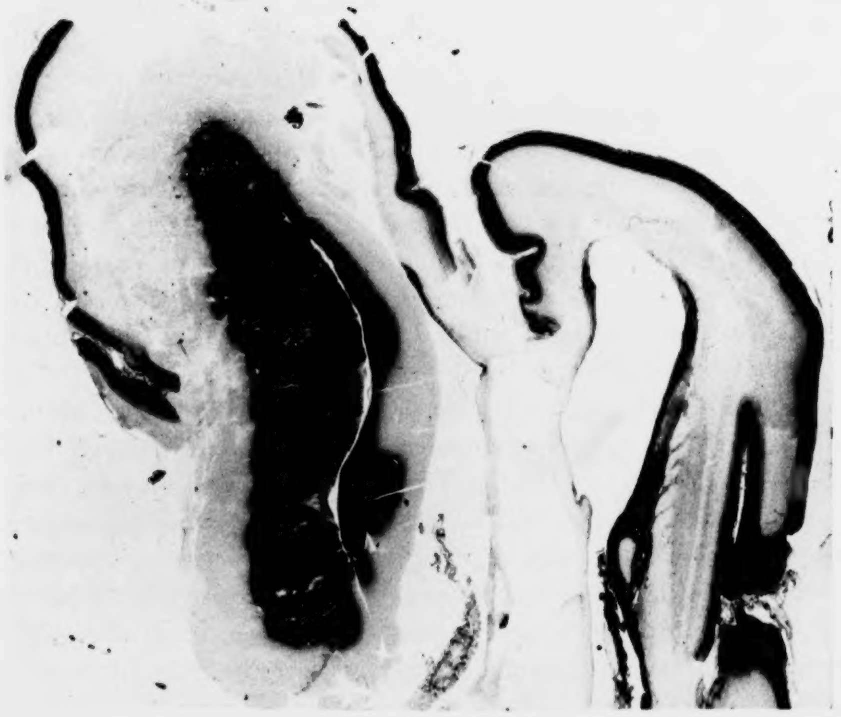


Figure 12—Massive cerebral hemorrhagic infarction in stillborn seven-month fetus; thrombosis of the internal cerebral veins evident in serial whole-brain histologic sections. Maternal history of vaginal bleeding; premature detachment of placenta. (B–265 WAM).

ized visceral congestion is present at necropsy in premature infants with cerebral periventricular infarctional damage and intraventricular hemorrhage and in other forms of neonatal hypoxic brain damage (Grontoft, Cruickshank, Ross).

(3) Local venous infarction of the cerebrum and other organs occurs in the hypoxic fetus and neonate, both in the premature and term infant, with greater frequency than is generally realized. Although such lesions occur at times in the kidney, intestines, and other organs, the most common site by far in the neonate is the cerebrum (Towbin 1964; MacGregor, 1960; Cruickshank; Ross and Dimmette; Schwartz; Craig; Larroche). The relationship of deep cerebral vein thrombosis and the occurrence of deeply placed, hemorrhagic, necrotic infarctional lesions in premature infants has been pointed out in the past (Ehlers and Courville; Schwartz; Kalbag and Woolf). With stagnation of venous blood flow, with or without thrombosis, cerebral tissue readily undergoes diffuse and local infarctional damage in the neonate; in the premature the periventricular germinal matrix tissue and neighboring structures are the primary target; in the term infant, the cortex proves most vulnerable to infarctional damage.

The severity of the periventricular infarction in the premature cerebrum and the subsequent intraventricular hemorrhage are in large measure governed by the pace of the underlying gestational or parturitional complication; if the hypoxic event, the disorder in the maternal-placental-fetal-neonatal organization, develops rapidly, as in sudden intrauterine compression of the umbilical cord, fetal death may occur before tissue changes can be imprinted in the brain or other organs. In such circumstances, the process of congestive failure, infarction, and hemorrhage may not be manifest; thus, paradoxically, many premature infants born after catastrophic intrauterine asphyxial complications show few organic hypoxic changes. If, however, oxygen deprivation in the fetus is gradual and protracted, as in slowly expanding placental detachment, or as in the premature postnatally with advancing pulmonary disorders, the interval of time involved permits a correspondingly gradual proliferation of matrix infarction and spreading of subependymal hemorrhage.

Subependymal matrix infarction at times takes place before birth, but rupture of the hemorrhagic lesion into the ventricle may be delayed for hours or days, ultimately occurring postnatally. The escape of blood may be slow and oozing, or may develop suddenly and be massive. The pathologic sequence correlates closely with the clinical course: The premature neonate, hypoxic at birth, showing mounting evidence of circulatory failure, may suddenly become unresponsive, abruptly go into shock, and expire—the agonal event reflecting the eruption of a hemorrhagic subependymal infarct, with sudden rapid intraventricular exsanguination.

The temporal factor indicated in the present studies—autopsy evidence that the processes leading to neonatal deep cerebral infarctional damage are essentially of intrauterine origin—is of pointed clinical importance. The danger to the premature, paradoxically, is that he will be delivered too early and too late. In many cases, after unrelieved intrauterine hypoxia, the underlying process leading to intracerebral damage is far advanced by the time the affected infant, moribund, is delivered. This matter is of critical concern obstetrically. In the last trimester of pregnancy, in cases in which placental or other fetal hypoxic gestational complications appear, the clinical practice of watchful waiting—until evidence of fetal distress, until signs of failing cardiac function are manifest—deserves reconsideration.

Cortical cerebral venous infarction at term. In contrast to the pattern of deep cerebral infarctional damage characteristic of the premature, in the mature fetus and newborn the cortex is the most frequent site of hypoxic cerebral damage (fig. 13). As the fetus matures and approaches term, the momentum of histogenesis at the core of the cerebrum declines; the subependymal germinal matrix tissue becomes reduced. On the other hand, in the cerebral cortex at this time architectural activity is intensified. The cerebral convolutional pattern is evolved, and the cortical laminar structure is differentiated. The predominance of the deep venous system of the cerebrum is in large measure displaced by the rapidly developing superficial system of cerebral veins spreading over the cortical surface. Correspondingly, near term, the site of hypoxic cerebral infarctional damage shifts from the deep, periventricular strata to the actively proliferating, vascularized cortex. The pathogenesis of cortical damage in the term neonate is analogous to the deep cerebral damage in the premature—in both, the damage is the consequence of hypoxic circulatory failure, with venous stasis-thrombosis leading to local infarctional damage (Table 4).

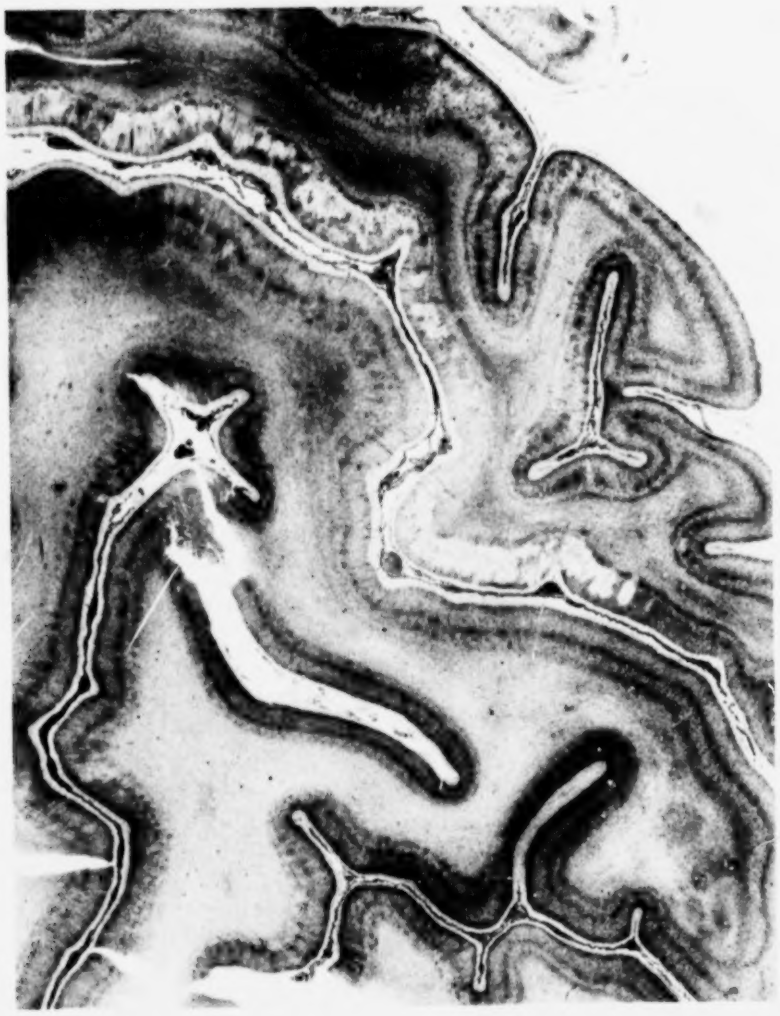


FIGURE 13—Diffuse cortical cerebral infarctional damage; laminar necrosis. Stillborn, slightly macerated, term infant. Placenta showed extensive retroplacental hematomas. (W–18 WAM).

In the term neonate, with stasis of circulation in the pial veins, the cortex at times shows patchy devastation (fig. 13), in some instances of laminar pattern. A less destructive form of cortical damage occurs at term when the hypoxic complication is less severe; hypoxic neuronal damage (ischemic neuronal necrosis) may affect broad areas of the brain. These cellular changes are most readily recognized in ther precentral cortex; the Betz cells may show all stages of hypoxic neuronal alteration, including eosinophilia of cytoplasm, eccentric displacement, and pyknosis of nuclei, as well as shrinkage and disintegration of cells. The Purkinje cells of the cerebellum also readily react to hypoxia in the neonate; the pyramidal cells of Ammon's horn are curiously unresponsive in the neonate.

In the fetus near term hypoxic damage in the cerebrum tends to be located in the upper middle strata of the hemispheric wall (fig. 14); the damage extends from the cortex inward; cortical and subcortical veins are prominently congested. The periventricular stratum of the cerebrum is relatively unaffected. The subcortical white matter and intermediate strata of the hemispheric wall may show

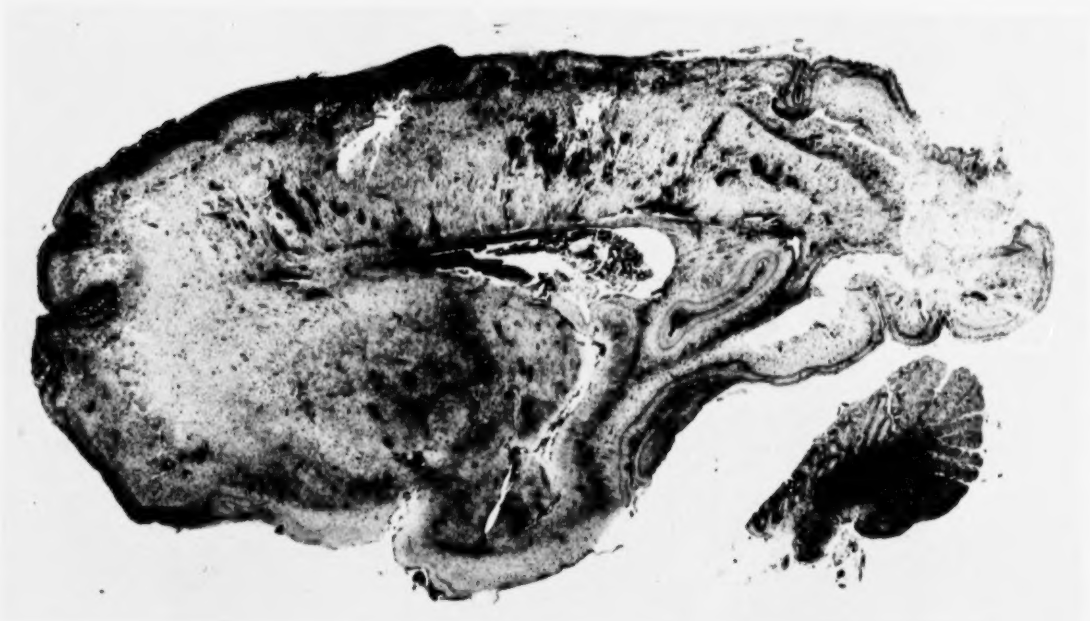


FIGURE 14—Cortical-subcortical cerebral venous infarction; infant stillborn at 34 weeks' gestation; smaller of twins; intrauterine "transfusion" syndrome associated with twin pregnancy and placental vascular shunt.

areas of frank infarction, with the overlying cortex being destroyed or showing laminar necrosis.

The incidence pattern of cerebral hypoxic damage is significant. Infarctional damage in the premature is of far greater occurrence than in the term infant, reaching its highest incidence at 28 weeks gestation (Tlppö). In the present material, of 140 technically sutable cases available between the gestational age of 22 and 35 weeks, severe infarctional lesions with hemorrhage were present in the deep cerebral structures in 26; lesions of moderate severity were present in 41; cerebral congestion with small hemorrhages was present in the remaining 73.

In 110 term or near term neonatal brain specimens, severe damage, mainly cortical, was present in only five cases. It bears emphasis that the occurrence of prematures with extensive deep cerebral hypoxic lesions is over ten times greater than the occurrence of term cases with cortical devastation.

Subacute Cerebral Infarctional Damage in the Fetus and Newborn

Subacute cerebral infarctional damage provides an important link pathologically in relating the processes of acute neonatal cerebral damage to the chronic lesions found in mental retardation.

Destruction of cerebral germinal matrix in the premature fetus and premature, per se, is not a lethal process. The hemorrhagic infarcts of the matrix may be small and localized, and the damage may remain latent. In stillborn premature infants and some premature infants who live for a short period and die of other organic causes, at times there are found circumscribed focal areas of necrosis and tan discoloration in the subependymal areas, especially at the caudothalamic groove, at the site previously occupied by germinal matrix deposits. The focal subependymal lesions are of subacute nature, histologically showing gliosis and the presence of hemosiderin-laden phagocytes. On the other hand, the damage incurred in utero may be extensive; at autopsy, infants born at term sometimes show massive destruction of the periventricular layers of the hemispheric wall. The damage is of subacute character pathologically and is plainly the result of hypoxic processes early in the last trimester of gestation.

The following case is an example of extensive subacute periventricular cerebral infarction (fig. 15). The mother became acutely ill two months before delivery with a respiratory infection and vaginal bleeding and required hospitalization. The pregnancy was maintained. The infant was delivered at term, weighed 2,770 gm, and lived 18 hours. Externally the infant appeared well formed; the head was of proportionate size. The brain was very small, weighing 130 gm. The miniature cerebrum showed well defined convolutions, giving the specimen the appearance of a collapsed loaf of braided bread. The histologic sections clearly indicated the mechanism of the damage; the vena galen and its deep cerebral tributaries contained well established thromboses; the periventricular layers of the cerebrum were destroyed by multiple confluent infarcts undergoing organization and scarring. The cerebrum appeared reamed out by the infarction, leaving the hemispheres as irregular thin-walled sacs covered with distorted cortical tissue.

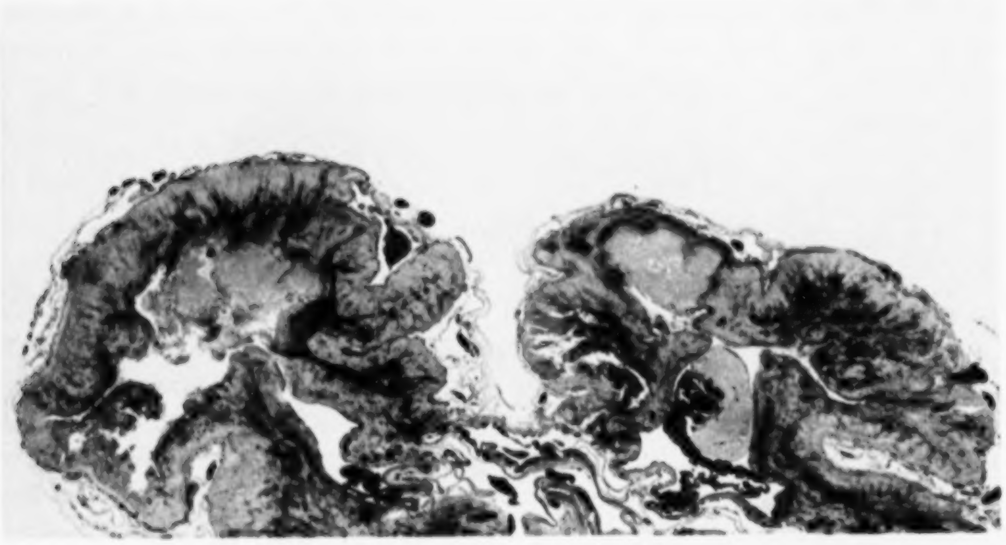


FIGURE 15—Subacute neonatal cerebral periventricular venous infarction; vena galen thrombosis present. History of maternal illness with vaginal bleeding, requiring hospitalization two months before delivery. Term infant, lived 18 hours. Brain weighed 130 gm (average, 360 gm). Section shows active advanced infarction with organization and scarring of periventricular tissue. (T–1).

Neonatal leucoencephaloclastic damage of this degree, advancing from the subacute stage of infarction to the chronic form in surviving infants, may ultimately result in the formation of multiple cavities and scarring in the deep, periventricular cerebral white matter (fig. 16). In extreme cases it may terminate with hydranencephaly, with small cerebral hemispheres of thin leather-like character covered with remnants of cortical tissue.

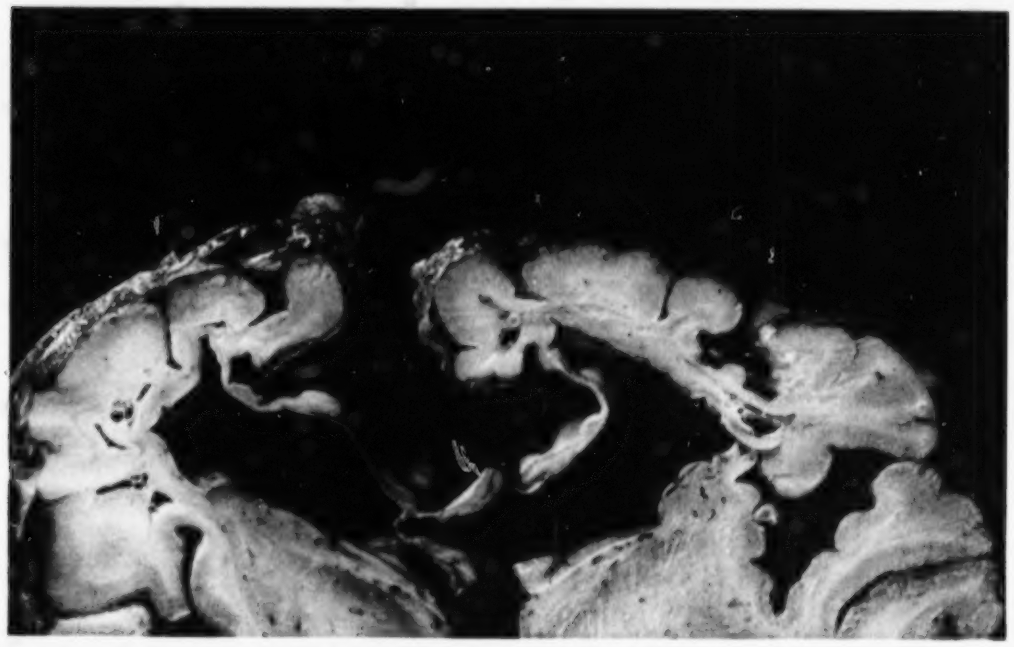


FIGURE 16—Chronic periventricular cerebral necrosis; characteristic pattern of brain damage in organic mental retardation and cerebral palsy. Seven-year-old spastic quadriplegic with mental retardation. (Compare with fig. 15). (CSS 5064).

Chronic Sequelae of Neonatal Brain Damage: Cerebral Lesions in Mental Retardation

The most significant sequelae of neonatal nervous system damage contributing to organic mental retardation stem from deep cerebral infarctional lesions imprinted in the fetus and premature newborn. Other forms of cerebral damage, such as cerebral subdural hemorrhage, are relatively rare as the cause of pediatric nervous system disturbances. On the other hand, the late manifestations of occult neonatal spinal injury merit wider consideration.

The processes of gestation and birth expose the fetus and neonate to many hazardous complications. The frequency of sublethal damage—the organic attrition suffered by the fetus and newborn—often escapes consideration. For the fetus, during its marginal existence in utero and as it is pistoned down the birth canal and separated, some degree of hypoxic and mechanical damage to the nervous system is inescapable. Gestation and birth form an inexorable leveling mechanism; with the brain blighted at birth, the potential of mentation may be reduced from that of a genius to that of an average child, or less. The damage may be slight or great. Substantially, it is said, all of us have a touch of cerebral palsy and mental retardation.

In mental retardation and cerebral palsy two basic patterns of cerebral lesions, stemming mainly from hypoxic damage neonatally, have been described by Malamud and others: deep cerebral lesions, characterized by cystic damage and scarring, affecting white matter, basal ganglia, and other periventricular structures; cortical damage, characterized by uniform atrophy of cerebral convolutions.

Deep cerebral damage is far more frequent in mental retardation and cerebral palsy than cortical scarring. Significantly, the frequency of deep cerebral damage in cases of mental retardation is analogous to high incidence of deep cerebral damage observed in neonatal case material. As in the pathogenesis of deep cerebral infarctional damage in the premature, the chronic cerebral lesions in mental retardation in most instances are located in relationship to the deep cerebral venous drainage system. The architectural character of the cerebral lesions, common to the premature newborn and chronic cases, is demonstrated in figs. 15 and 16 and in figs. 11 and 17. The similarity in location of the lesions, in the periventricular strata, is not a random occurrence. Pathologically the lesions are of the same genesis; all are encephaloclastic and, viewed together, demonstrate the transition of acute, subacute, and chronic cerebral damage.

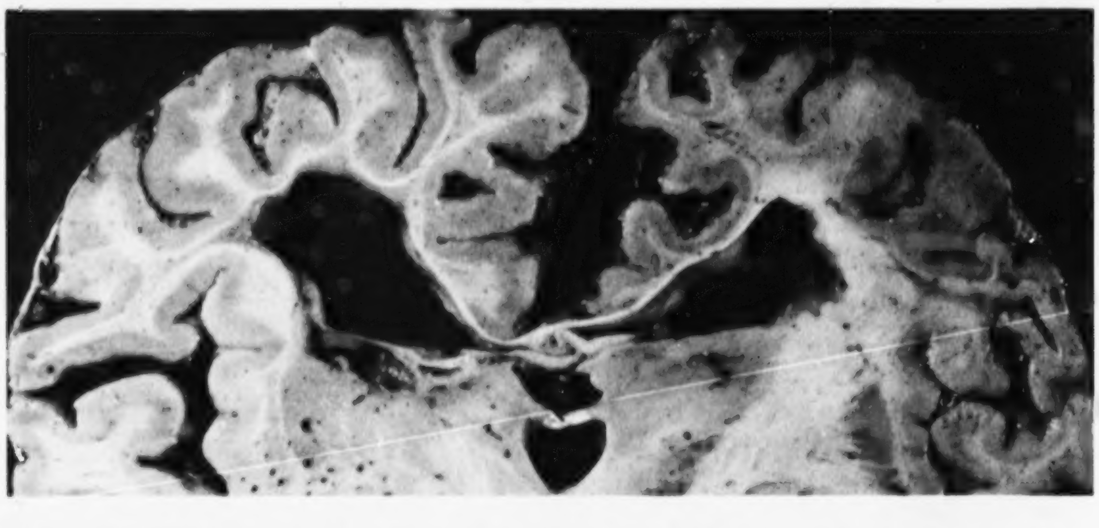


FIGURE 17—Chronic cerebral lesions in mental retardation; characteristic periventricular location; on the left, cystic areas of necrosis and scarring occupy the region near the caudo-thalamic groove, involving corpus striatum and thalamus; periventricular white matter decreased, especially in the upper lateral aspect of the hemispheric wall. Eight-year-old girl with mental retardation and spastic quadriplegia. (Compare with Figure 11). (CSS–10762).

Correlating the patterns of cerebral damage in the newborn with patterns of damage in mental retardation and cerebral palsy cases, we can devise a formula for the time of incurrence of the cerebral damage in the chronic case material: Lesions located in the periventricular structures reflect damage incurred at 22 to 35 weeks gestation, or earlier; destruction of cortex indicates damage incurred in the mature fetus or neonate.

The concepts derived here have a direct bearing on the problem of the high incidence of mental retardation and cerebral palsy in infants born prematurely, the neurologic deficits being attributable to precocious destruction of cerebral germinal matrix. Correlation of findings in this study yields information explaining the enigmatic occurrence of organic mental retardation and cerebral palsy in infants after uncomplicated delivery at term, the cerebral damage having been imprinted, often latently, weeks before birth, as indicated by its deep, periventricular location.

Applied in a broader sense, the findings in these current studies indicate that venous infarction of germinal matrix tissue, producing residues of chronic cerebral damage, is a basic mechanism of pathogenesis in mental retardation and related infantile brain disorders.

DISCUSSION

Doctor Yates: I agree with Dr. Towbin about his matrix lesions and the hemorrhages occurring on the venous cord. I think we're all converted there. I would argue that the cortical lesions, which to my mind, in both adult and infants have an arterial or a generalized ischemic cause, and are not necessarily venous at all.

There is another point. He did show us some venous thromboses, and venous thromboses do occur quite commonly secondarily to infarction, of an arterial kind. That is, when you've got dead tissue, the veins that drain the dead tissue often thrombose secondarily.

Doctor Malamud: If the question is venous versus arterial, I may have to vote for venous. The lesions that Dr. Towbin showed correspond nicely with those that I try to show.

The two ideas that he proposed that can be duscussed are, first of all, the idea of hypoxia as being the major factor in pathogenesis of the lesions and it seemed to me that Dr. Carlson threw some doubt into the area. The other, which is perhaps more significant, is that Dr. Towbin assumes that the lesions that we see at term are probably delayed effects or later effects of something that has happened weeks or months before that time.

Now, that would take away the impact of the obstetrical or the labor difficulties, which I think are central in the issue of the pathogenesis of those conditions that lead to cerebral palsy and mental retardation. I take issue with that. I think the problem is largely that of the stresses of labor and the moments preceding rather than an expression of a previous immaturity of tissue that leads to necrosis and to subsequent problems.

As you might recall, my statistics showed that in 70 percent of my material the lesions were in term deliveries, and not premature. So these two questions bother me and I'm not sure that we have the answers to them.

Doctor Trembath: J. L. Emery has described slowing growth at the costochondral junction of both premature and full-term infants dying in the immediate neonatal period. This evidence supports the hypothesis of intrauterine distress which, when seen at a later point of time, may be interpreted as birth trauma.

Doctor Caldeyro-Barcia: I have one problem—When I see the diagnosis of hypoxia or anoxia, few measurements of oxygen have been made. I think that this creates confusion. I would make a plea that these diagnoses be revised and only used when the criteria are generally recognized, and that they not be employed in cases where hypoxia may not have been present or was not the dominant disturbance.

This is one point: Today it is possible to measure these properties of the blood. The measurements can be made accurately and, in addition to hypoxia, other changes can and should be included.

Another point is this: Studies made on monkeys by Wendell, Meyers, and others do not support the hypoxic or anoxic theory of brain hemorrhage. In acute asphyxia, as done by Wendell, no hemorrhage was found in the central nervous system. In studies by Meyers no deep hemorrhage was found, only some hemorrage on the surface of the brain. So I would like to know, what is the evidence supporting the hypoxic or anoxic theory of brain damage?

Participant: I'd like to ask Dr. Towbin, what were the smallest infants in which he observed the thromboses? There is very good evidence that in fetuses up to about 12 centimeters, the blood doesn't clot at all. How early does he think that some of these processes start?

Doctor Towbin: I'll answer the last question first by saying that I don't think this is the time to get into that swamp of defining what a thrombosis is. When we look at these vessels, in all honesty we say that they are thromboses, but sometimes we're more sure of it than at other times. As for measuring anoxia, with all due respect, I think the pathologist is in a very good position to interpret anoxia from what he sees. I think that we have just as good a basis for diagnosing it as you do with your machinery. When the infant is cyanotic and has a big liver, a big spleen, this is the picture of an asphyxial death, and this is the label that is put on it, not by me, but as observed by Dr. Alvord and Dr. Clifford. I think we're right.

I think that when you say anoxia, we all know we're talking about many things and it's just a label. It's that thing that goes with asphyxia. I don't have any issue really with Dr. Malamud's comment about this being a postnatal pattern. The lesion in the term infant is like the lesion one sees in infants who are born at term and develop these lesions a week or a month later. They are cortical lesions. The term infant responds as does an adult or a postnatal child. Just as it is extremely rare to find deep venous thromboses in the adult (this is the province of the premature, so is it rare to find it in the term infant.

I think, Dr. Malamud, that it is incontestable that when one finds such lesions in slightly macerated fetuses, there are many cases in which these lesions were imprinted before labor. I don't think that there is any other way to interpret this. I think that this does mean, that these are prenatal processes. In some cases, certainly, some of them carry through the intranatal period and postnatal period, but in a very big, important group, maybe most, the heart of this process is prenatal. This has to be worked on, of course, but I think this is the direction in which we will move.

Doctor Carlson: How could we test to see if anoxia were present? At the time we get these infants– It has been said that the preemie is born too early and too late. I think if you really want a premature to live and you get a healthy premature (and we're very good at keeping prematures alive these days) then you are much better off with a preemie who has gestated for 35 weeks, who is not damaged by 5 days or 5 hours of hypoxia, than you are with one a week older but a moribund. If I may say so as a pathologist, the clinician, perhaps, waits too long sometimes. By the time he has evidence of cardiac changes, the infant is manifesting evidences of circulatory failure.

Doctor Clifford: I am going to try to answer Dr. Carlson's question. I didn't think that anybody alive today knew that I had written that paper in 1941. Since it does imply that I was talking about anoxia, as we call it, I might just get it on the record that we tried to use Nature's experiment. When a mother came in with active, vigorous bleeding (an active hemorrhage) and was not in labor, she was delivered by a Caesarean section. We had, over a period of time, a large series of these cases, I forget how many now, maybe 40 or 50. They were mostly ruptured placentas. Going over the autopsy material we found a pattern of congestion and edema and various types of hemorrage in all of the various organs, with destruction of tissue. This was the basis. It was assumed with this massive hemorrhage anoxia was the preceding factor.

REFERENCES

Arey, J. B., and Anderson, G. W.: "Pathology of the Newborn," in Greenhill, J. P.: *Obstetrics.* 13th ed. Philadelphia: W. B. Saunders, 1965, Ch 70, pp 982–1022.

Banker, B. Q., and Larroche, J. C.: Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. *Arch Neurol 7: 386–416 (Nov) 1962.*

Clifford, S. H.: The effects of asphyxia on the new born infant. *J. Pediat 18: 567–578. (May) 1941.*

Coutelle, C.: Uber epidurale Blutungen in den Wirbelkanal bei Neugeborenen und Säulingen und ihre Beziehung zu anderen perinatalen Blutungen. *Z Geburtsh Gynaek 156: 19–52, 1960.*

Craig, W. S.: Intracranial haemorrhage in new-born; study of diagnosis and differential diagnosis based upon pathological and clinical findings in 126 cases. *Arch Dis Child 13:89–124 (June) 1938.*

Crothers, B.: Changes of pressure inside the fetal craniovertebral cavity. *Surg Gynec Obstet 37: 790–801 (Dec), 1923.*

Crothers, B.: Injury of the spinal cord in breech extraction as an important cause of foetal death and of paraplegia in childhood. *Amer J Med Sci 165:94–110, (Jan) 1962.*

Crothers, B., and Putman, M. C.: Cord birth injuries. *Birth Injuries of the Central Nervous System,* (ed.), F. R. Ford, Baltimore: Williams & Wilkins, *1927,* pt. II, (Medicine Monographs)

Cruickshank, J. N.: *Child Life Investigations: The Causes of Neonatal Death.* Privy Council, Medical Research Council, Special Report Series No. 145. London: His Majesty's Stationery Office, 1930.

Ehlers, H., and Courville, C. B.: Thrombosis of internal cerebral veins in infancy and childhood; review of the literature and report of 5 cases. *J Pediat 8: 600–623, (May) 1936.*

Ehrenfest, H.: *Birth Injuries of the Child.* New York: Appleton-Century-Crofts, 1931.

Fodrel, V.: Die Halsmarkquetschung, eine Unterart der geburtstraumatischen Schädigung des Zentralnervensystems. *Arch Gynaek 143: 598–634, 1930.*

Ford, R. F.: *Diseases of Nervous System in Infancy, Childhood, and Adolescence.* Charles C Thomas, Springfield, Ill., 1950.

Ford, F. R.: *Diseases of the Nervous System in Infancy, Childhood, and Adolescence.* ed 4, Springfield, Ill.: Charles C Thomas, 1960.

Gröntoft, O.: Intracranial haemorrhage and blood-brain barrier problems in the new-born. *Acta Path Microbiol Scand, Suppl. C, 1954.*

Hausbrandt, F., and Meier, A.: Zur Kenntnis der geburtstraumatischen und extrauterin erworbenen Schäden des Zentralnervensystems bei Neugeborenen. *Frankfurt Z Path 49:21–62, 1936.*

Hellström, B., and Sallmander, U.: Prevention of spinal cord injury in hyperextension of the fetal head. *JAMA 204: 1041–1044 (June 17), 1968.*

Kalbag, R. M., and Woolf, A. L.: *Cerebral Venous Thrombosis;* With Special Reference to Primary Aseptic Thrombosis. London: Oxford Univ. Press, 1967.

Knowlton, R. W.: Flying fetus. *J Obstet Gynaec Brit Comm 45: 834–835 (Oct) 1938.*

Larroche, J. C.: Hémorrhagies cérébrales intra-ventriculaires chez le premature. I. Anatomie et physiopathologie. *Biol Neonat 7: 25–56, 1964.*

Litzmann, C. C. T.: Ein Beitrag zur Kenntnis der spinalen Lähmung bei Neugeborenen. *Arch Gynaek 16: 87–106, 1880.*

Macgregor, A. R.: The pathology of still-birth and neonatal death; review of 1053 cases. *Brit Med Bull 4: 174–178, 1946.*

Macgregor, A. R.: *Pathology of Infancy and Childhood.* Edinburgh: E. & S. Livingston Ltd., 1960.

Malamud, N., *et al.*: An etiologic and diagnostic study of cerebral palsy. A preliminary report. *J Pediat 65: 270–293, (Aug), 1964.*

Manterola, A.: Towbin, A.; and Yakovlev, P. I.: Cerebral infarction in the human fetus near term. *J Neuropath Exp Neurol 25: 479–488, (Jul), 1966.*

Pierson, R. N.: Spinal and cranial injuries of baby in breech deliveries. *Surg Gynec Obstet 37: 802–815, (Dec), 1923.*

Potter, E. L.: *Pathology of the Fetus and Infant ed 2.* Chicago: The Year Book Medical Publishers, 1961.

Ross, J. J., and Dimmette, R. M.: Subependymal cerebral hemorrhage in infancy. *Am J Dis Child 110: 531–542, (Nov), 1965.*

Ruge, C.: Uber die Verletzungen des Kindes durch die Extraction bei Ursprünglicher oder durch Wendung herbeigeführter Beckenendelage nebst kurzer Beleuchtung der Extractions, *Z Geburtsh und frauenkr 1:69, 1875.*

Schwartz, P.: *Birth Injuries of the Newborn; Morphology, Pathogenesis, Clinical Pathology and Prevention.* New York: Hafner, 1961.

Stoltzenberg, F.: Zerreissungen der intervertebralen Gelenkkapseln der Halswirbelsäule eine typische Geburtsverletzung. *Berlin Klin Wschr 48: 1741–1743, 1911.*

Toverud, K. U.: Etiological factors in neonatal mortality, with special reference to cerebral hemorrhage. *Acta Paediat Scand 18: 249–271, 1936.*

Towbin, A.: The pathology of cerebral palsy. I. Developmental defects of the brain as a cause of cerebral palsy. II. Cerebral palsy due to encephaloclastic processes. *Arch Path 59:397, 529, 1955.*

Towbin, A.: *The Pathology of Cerebral Palsy.* Springfield, Ill.: Charles C Thomas, 1960.

Towbin, A.: Spinal cord and brain stem injury at birth. *Arch Path 77: 620–632, (June), 1964.*

Towbin, A.: "Massive cerebral hypoxic damage in the human fetus near term." *Proc Fifth Internat Congr Neuropath;* Excerpta Med. Internat. Congr. Series No. 100, 1965, pp 724–729.

Towbin, A.: Cerebral intraventricular hemorrhage and subependymal matrix infarction in the fetus and premature newborn. *Amer J Path 52: 121–140 (Jan), 1968.*

Towbin, A.: Cerebral hypoxic damage in fetus and newborn: Basic patterns and their clinical significance. *Arch Neurol. 20:35–43 (Jan) 1969.*

Towbin, A.: Neonatal neuropathologic autopsy. *Neuropathology: Methods and Diagnosis,* (ed.) C. G. Tedeschi. Boston: Little, Brown Co., in press.

Volbert, H., and Schweitzer, H.: Uber Häufigkeit, Lokalisation und Atiologie von Blutungen im Wirbelkanal bei unreifen Früchten und Frühgeburten. *Geburtsh Frauenheilk 14: 1041–1048 (Nov), 1954.*

Yates, P. O.: Birth trauma to the vertebral arteries. *Arch Dis Child 34: 436–441, (Oct), 1959.*

Yippö, A.: Pathologisch-anatomische Studien bie Frühgeburten, *Z Kinderheilk 20: 212–431, 1919.*

Zellweger, H.: Uber Geburtstraumatische Rückenmarkslaesionen. *Helv Paediat Acta 1: 13–29, (Aug), 1945.*

THE CLINICAL EVALUATION OF THE LOW-BIRTH-WEIGHT INFANT WITH REGARD TO HEAD TRAUMA

Murdina M. Desmond, M.D.
Arnold J. Rudolph, M.D.
Newborn Section, Department of Pediatrics
Baylor University College of Medicine and
Jefferson Davis Hospital
Houston, Texas

For clinicians whose patients are the newly born, these are exciting times. Knowledge of the complex process of extrauterine adaptation is accumulating at an extraordinary rate. Yet we are aware of unresolved problems. Nursery records continue to be unsatisfactory sources for later study. We need to define the entities comprising neonatal morbidity. As Smith notes, nursery areas have problems but few clear-cut diagnoses.

Evaluation of the newly born infant in this manner introduces complexities, as the infant, a first encounter, is positioned at some point in a sequence of rapid physiologic change and since much of his past experience (the course through pregnancy, labor and delivery) is only incompletely known (fig. 1).

Morbidity may be defined as evidence of dysfunction or intrinsic disease at any point in the life span of an individual. This definition applies also to the neonate.

In examining the infant from the point of view of trauma to the central nervous system, one must differentiate between anatomic residua (Table 1) and functional changes (Table 2). Functional changes in turn, may be transitory (following closely upon delivery), may be related to gestational age, to pharmacologic influences, or may be clearly abnormal.

The extent of neonatal morbidity in a consecutive series of 6,211 full-size and small infants is shown in tables 3 and 4.

Morbidity occurring in the labor and delivery area was considered separately from that of the nursery. In the labor and delivery room, 32 percent of births, or 1 in 3 infants born alive, gave some evidence of morbidity; abnormalities of fetal heart tones, premature onset of bowel function, failure of arousal, abnormal respiration, shock, and failure to maintain respiration. All of these problems ultimately represent dysfunction of the nervous system as affected by asphyxia, trauma, maternal medications, malformations, and other adverse intrauterine experiences. As would be expected, delivery room morbidity was higher in the infant of low birth weight.

Supported by the John A. Hartford Foundation, Inc.

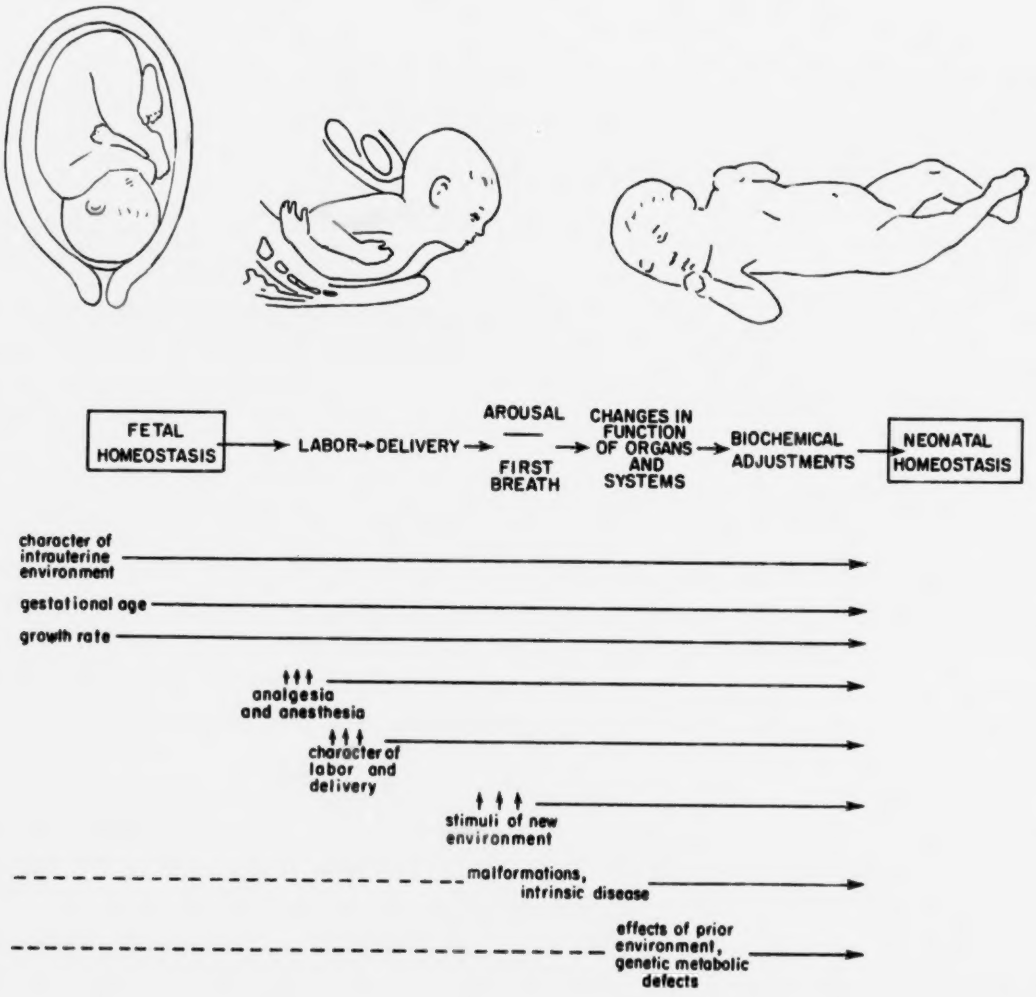

FETAL HOMEOSTASIS
LABOR→DELIVERY
AROUSAL
FIRST BREATH
CHANGES IN FUNCTION OF ORGANS AND SYSTEMS
BIOCHEMICAL ADJUSTMENTS
NEONATAL HOMEOSTASIS
character of intrauterine environment
gestational age
growth rate
analgesia and anesthesia
character of labor and delivery
stimuli of new environment
malformations, intrinsic disease
effects of prior environment, genetic metabolic defects

FIGURE 1.—The course of events ensuing between fetal homeostasis and neonatal homeostasis. Factors influencing the sequence are shown in the lower portion of the diagram.

TABLE 1.—*Residua of labor and delivery visible in live infants*

- Molding of skull or body
- Skull depression
- Caput succedaneum or edema and congestion of presenting part
- Cephalhematoma
- Massive scalp hemorrhage (subgaleal bleeding)
- Scalp necrosis
- Scleral or retinal hemorrhage
- Petechiae
- Ecchymoses
- Hematoma
- Contusion
- Abrasion
- Laceration
- Fat Necrosis
- Fracture (skull, clavicle, extremity)
- Peripheral palsy

In the nursery area, morbidity was found in 1 of every 4 infants (23 percent) during their nursery stay. This represents 1 of 5 to 6 term infants (17 percent) and 1 of 2 infants of low birth weight (58.8 percent).

Table 2.–*Clinical findings in infants of low birth weight*

MAY BE TRANSITORY

(Immediately Following Birth:)

- Hypotonus
- Inactivity
- Poor reflex response
- Grunt in response to variety of stimuli (tactile, thermal etc.)
- Subcostal retraction
- Poor peripheral circulation

MAY BE RELATED TO IMMATURITY

- Hypotonus
- Periodic respiration
- Apneic pauses associated with random movements
- Random movements
  - grimacing, twitching, pursing, myoclonic jerks
- Poorly sustained sucking response
- Subcostal retraction
- Vasomotor instability

MAY BE PHARMACOLOGIC EFFECTS

- *Meperidine, barbiturates*
  - shallow respiration, inactivity, poor suck or swallow, diminished bowel sounds, brief reflex response
- *Reserpine*
  - bradycardia, increased tone, vasodilation, tremors, hyperperistalsis
- *Diazepam*
  - decreased tonus
- *Phenothiazine.*
  - decreased tonus, vasomotor instability

ABNORMAL FINDINGS

Cardiopulmonary

- Shock
- Abnormal respiration—labored, gasping, gulping, grossly irregular, panting
- Arrythmias
- Fixed heart rate
- Extreme changes in blood flow

Apneic or Cyanotic Episodes

Neurologic

- Cry—weak, whining, shrill, outcries, aphonia
- Full fontanelle
- Tonus—hypotonus, flaccidity, hypertonus, rigidity, asymmetry
- *Movement*
  - Absent spontaneous movement
  - Immobility alternating with motor restlessness
  - Loss random movements
  - Stereotyped movements
  - Constant toe flexion or extension
  - Wide amplitude tremors
  - Poor suck or swallow
  - Expression—open eyed stare, frowning, anxious
  - Pupils—pinpoint, dilated, irregular, loss corneal reflex
  - Loss automatisms and mass reflexes
- *Convulsions*
  - Clonic, tonic
- Repetitive movements—nystagmoid, rolling and myoclonic jerks of eyes
  - Chewing

Unstable Body Temperature

All illnesses in the nursery, however transitory, were included in the total morbidity. They may be grouped according to congenital malformation (major, minor, positional), abnormal respiration, CNS depression, neurologic abnormalities other than depression, jaundice (all levels), bleeding, tissue injury, infections, and a large group of intrinsic disorders and transitional problems (delayed passage of meconium, feeding difficulties, vomiting, etc.). Half the infants who were considered ill had some nervous system component to their illness.

Relating morbidity to all the forces and stimuli impinging on the fetus during labor and delivery is a difficult task. To consider the possible role of trauma, we may examine the morbidity occurring after a potentially traumatic type of delivery–breech presentation (Tabl 3) or, in association with one type of tissue injury, ecchymosis (Table 4).

TABLE 3.—*The incidence of abnormal clinical findings in a nursery population compared with the incidence in infants born by breech presentation*

	TERM LIVE BORN INFANTS Birth Weight 2501 Grams Or More				INFANTS OF LOW BIRTH WEIGHT Birth Weight 2500 Grams Or Less			
	CONSECUTIVE TERM LIVE BIRTHS		WITH BREECH PRESENTATION		CONSECUTIVE LBW LIVE BIRTHS		WITH BREECH PRESENTATION	
	5300		150		911		114	
	No.	%	No.	%	No.	%	No.	%
DELIVERY ROOM								
Low 1-minute Apgar Score (0–6)	718	(13.5)	73	(48.7)	363	(39.8)	86	(75.3)
Deteriorated after one minute	45	(0.8)	2	(1.3)	28	(3.1)	7	(6.1)
Ventilatory Assistance Required	224	(4.2)	29	(19.3)	200	(22.0)	53	(46.5)
Endotracheal Intubation	159	(3.0)	15	(10.0)	144	(15.8)	36	(31.6)
NURSERY								
Abnormal Respiration (All Types)	153	(2.9)	12	(8.0)	322	(35.3)	57	(50.0)
Apneic Attacks	16	(0.3)	2	(1.3)	128	(14.1)	26	(22.8)
Abnormal CNS Signs	454	(8.6)	30	(20.0)	227	(24.9)	30	(26.3)
CNS Irritation	224	(4.2)	17	(11.3)	109	(12.0)	14	(12.3)
Convulsion	21	(0.4)	5	(3.3)	35	(3.8)	6	(5.3)
Depression	285	(5.3)	20	(13.3)	187	(20.5)	30	(26.3)
Infection	99	(1.9)	11	(7.3)	167	(18.3)	17	(14.9)
Hyperbilirubinemia (above 12 mgms. %)	46	(0.9)	4	(2.7)	98	(10.8)	12	(10.5)
MAJOR MALFORMATIONS	140	(2.6)	7	(4.7)	34	(3.7)	4	(3.5)
NEONATAL DEATHS	25	(0.5)	3	(2.0)	112	(12.3)	29	(29.4)

Table 4.—*Clinical findings in a nursery population related to the presence or absence of ecchymoses*

	TERM LIVE BORN INFANTS Birth Weight 2501 Grams Or More				INFANTS OF LOW BIRTH WEIGHT Birth Weight 2500 Grams Or Less			
	ALL LIVE BIRTHS		WITH ECCHYMOSES		ALL LIVE BIRTHS		WITH ECCHYMOSES	
	5300		115		911		69	
	No.	%	No.	%	No.	%	No.	%
DELIVERY ROOM								
Low 1-minute Apgar Score (0–6)	718	(13.5)	38	(33.0)	363	(39.8)	47	(68.1)
Deteriorated after one minute	45	(0.8)	1	(0.9)	28	(3.1)	5	(7.2)
Ventilatory Assistance Required	224	(4.2)	14	(12.2)	200	(22.0)	32	(46.3)
Endotracheal Intubation	159	(3.0)	10	(8.7)	144	(15.8)	23	(33.3)
NURSERY								
Abnormal Respiration (All Types)	153	(2.9)	10	(9.6)	322	(35.3)	48	(69.6)
Apneic Attacks	16	(0.3)	2	(1.7)	128	(14.1)	31	(44.9)
Abnormal CNS Signs	454	(8.6)	27	(23.5)	227	(24.9)	60	(84.0)
CNS Irritation	224	(4.2)	15	(13.0)	109	(12.0)	16	(23.2)
Convulsion	21	(0.4)	2	(1.7)	35	(3.8)	8	(11.6)
Depression	285	(5.3)	21	(19.1)	187	(20.5)	33	(47.9)
Infection	99	(1.9)	3	(2.6)	167	(18.3)	17	(24.6)
Hyperbilirubinemia (above 12 mgms. %)	46	(0.9)	2	(1.8)	98	(10.8)	20	(29.9)
MAJOR MALFORMATIONS	140	(2.6)	9	(7.8)	34	(3.7)	3	(3.4)
NEONATAL DEATHS	25	(0.5)	1	(0.9)	112	(12.3)	24	(34.8)

In infants delivered by breech presentation, over-all morbidity is doubled. In the low-birth-weight infant it is increased, but not to the extent seen in the term infant. Death rates are high in both groups.

When infants demonstrate ecchymosis or visible bruising, the over-all morbidity is also higher. In this instance we cannot state that the forces involved in labor and delivery were excessive, but rather that the tissues of this particular infant could not withstand them. Infants with intrauterine infection or hemolytic disease of the newborn may show widespread ecchymosis after a labor and delivery that appear physiologic in all respects.

Bleeding or tissue injury (anatomic residua of the birth process) occurred in 9.2 percent of all births, 7.9 percent of term births, and 15.6 percent of infants of low birth weight. Important as visible anatomic tissue injury or bleeding may be, it is not always associated with disturbance of function, which is of prime importance in evaluating the short- or long-term effects of labor and delivery on the child.

The clinician cannot evaluate one variable—trauma—apart from the multiple variables involved in labor and delivery. He can, however, and must for the purposes of management, decide at a specific point in time whether the infant is or is not functioning normally.

Faced with neurologic signs, he may ask the following questions: Are these signs transitory and related to the birth process? Are they related to gestational age? Are they effects of antenatal medications or intrauterine posture? Or is there clear indication of a disturbed central nervous system?

Findings requiring differentiation (Table 2) are given below:

Transitory Findings. Birth in the immature infant, as in his mature counterpart, is followed by tachycardia, rapid respiration (interrupted by grunting), alerting behavior, and a fall in body temperature. (Desmond and colleagues.) The term infant shows a brief period of hypertonus not present in the immature. Rudolph has stated that the immature infant not infrequently appears transiently flaccid at delivery. A 5- to 15-minute interval may occur before the onset of tachycardia. Alerting behavior may be brief.

With thermal or tactile stimuli, grunting and retraction may be present. A sluggish peripheral circulation is present during the first 24 to 48 hours. Gesell and Escardo have noted the unreliability of reflex responses during the first 24 hours of life.

Findings Related to Immaturity. General hypotonus is seen in the infant of under 32 weeks gestation. Sucking is poorly sustained. Subcostal retraction is physiologic. After 24 to 48 hours, periodic respiration with apneic pauses associated with movements of random distribution may be prominent. Movements are fleeting (grimace, purse, twitch) and myoclonic in nature. The site at which movement occurs is variable and not often predictable.

Koenigsberger and Robinson have stated the importance of separating findings compatible with gestational age from those that are not to be expected. Recent handling (feeding, multiple procedures) may precipitate hypotonus and apnea in the immature.

Persistence of Intrauterine Posture. During intrauterine life, movement of extremities, head, etc., may be limited and posture distorted. Browne has reported that after birth these postures may be temporarily maintained, leading to localized hypertonus and asymmetry of posture and movement. Infants born after prolonged rupture of the membranes, or by abnormal presentation, may likewise present temporary aberrations of posture, tone and movement.

Pharmacologic Effects. Respiratory depression of moderate degree may be recognized in the infant after administration of meperidine, barbiturates, or general anesthesia to the mother. Moderate depression associated with shallow respiration, absence of deep breaths, inactivity, brief or poorly sustained reflex response, and delay in passage of meconium has been described by Desmond, Rudolph, and Phitaksphraiwan. (Severe depression associated with poor gaseous exchange is more difficult to identify as an entity apart from the effect of asphyxia).

Rauwolfia compounds given antenatally may produce hypertonus, bradycardia, nasal stuffiness, episodic dyspnea, tremors, and low body temperature. These effects would not be expected to alter 1-minute Apgar scores, since they become evident some hours after delivery. The duration seldom exceeds 2 to 5 days.

Diazepam, as an analgesic, may be associated with moderate hypotonus in the infant at the time of delivery, although there is no biochemical evidence of depression. This effect is no longer present in the majority of infants after 24 hours, Flowers has noted.

Phenothiazines given antenatally may be associated with transient hypotonus (Crawford), inactivity, and vasomotor instability in the infant. After chronic high dosage late in pregnancy, the infant may show altered clinical behavior of two types: depression, beginning after delivery and lasting from hours to 3 days; and agitation, tremors, hand posturing, and hypertonus, a phase of variable duration from weeks to months (Hill, et al., Desmond, et al.).

Findings considered clearly abnormal and possibly indicative of central nervous system dysfunction are outlined in table 6.

Abnormal respiration concomitant with evidence of CNS depression is the most frequent clinical syndrome encountered in low-birth-weight infants, particularly the immature. When shock is present as well, it is usually not possible to distinguish infants with CNS hemorrhage (subarachnoid or intraventricular) from those with acute anemia, intrauterine pneumonia, septicemia, or asphyxial involvement, or from those whose abnormal respiration is idiopathic in origin. When the shock and asphyxia are treated, and if the infant improves, clinical manifestations may become more revealing.

A sudden apneic episode, with or without an outcry or convulsion, in an infant with prior mild to severe respiratory distress, is often associated with intraventricular hemorrhage at autopsy (Craig, 1938). A bulging or full fontanelle may be helpful in making this diagnosis. (An acute subdural hemorrhage must also be considered, although it is extremely rare).

A characteristic sequence of neurologic signs during life may be associated with kernicterus at autopsy, described by Gerrard and Van Praagh. In our experience, this progression of symptomatology may also occur in immature infants who have had severe birth asphyxia (without subsequent jaundice) and in infants with transplacental infection (e.g., rubella encephalitis) and intracerebral hemorrhage involving the periventricular areas.

In the term infant, cephalhematoma may occasionally be associated with anemia, jaundice, and signs of central nervous system irritation, but not in the great majority of instances. Underlying skull fractures are rare. In the immature subject, however, cephalhematoma is of serious import, and is linked with high morbidity and mortality.

Summary

At our present state of knowledge, it is difficult to relate nursery symptomatology directly to birth trauma. Before suggestive findings can be evaluated, the complete history of gestation, labor, and delivery must be reviewed, and the physical examination interpreted in terms of the age of the infant and his position in the transition sequence.

REFERENCES

Browne, D.: A mechanistic interpretation of certain malformations. *Advances in Teratology*, Vol. 2, 12–34, Logos Press, Ltd., 1967.

Craig, W. S.: Intracranial haemorrhage in the new-born: Study of diagnosis and differential diagnosis based upon pathological and clinical findings in 126 cases. *Arch Dis Child 13: 89–124 (June) 1938.*

Craig, W. S.: Intracranial irritation in the newborn: Immediate and long term prognosis. *Arch Dis Child 25: 325–350 (Dec) 1950.*

Craig, W. S.: Convulsive movements occurring in the first 10 days of life. *Arch Dis Child 35: 336–344 (Aug) 1960.*

Crawford, J. S.: Letters to the Editor: The Apgar Scoring System. *Develop Med Child Neurol. 4: 441–445 (Aug) 1962.*

Desmond, M. M., Franklin, R. R., Vallvona, C., Hill, R. M., Plumb, R., Arnold, H., and Watts, J.: The Clinical behavior of the newly born. I. The term baby. *J Pediat 62: 307–325 (Mar) 1963.*

Desmond, M. M., Rudolph, A. J., Hill, R. M., Claghorn, J. L., Dreessen, P. R., and Burgdorff, I.: Behavioral alterations in infants born to mothers on psychoactive medication during pregnancy. *Symposium on Congenital Causes of Mental Retardation.* Texas Institute of Mental Sciences. In press.

Desmond, M. M., Rudolph, A. J., and Phitaksphraiwan, P.: The transitional care nursery. A mechanism for preventive medicine in the newborn. *Pediat clin N Amer 13: 651–668 (Aug) 1966.*

Dotson, E., and Desmond, M. M.: The evaluation of muscle tonus in the newborn. *Neurology 14: 464–471 (May) 1964.*

Dreyfus-Brisac, C., and Monod, N.: "Electroclinical studies of status epilepticus and convulsions in the newborn," in Kellaway, P., and Petersen, I. (eds.): *Neurological and Electroencephalographic Correlative Studies in Infancy,* New York: Grune & Stratton, 1964.

Escardó, F., and de Coriat, L. F.: Development of postural and tonic patterns in the newborn infant. *Pediat Clin N Amer 7: 511–525 (Aug) 1960.*

Flowers, C. E., Rudolph, A. J., and Desmond, M. M.: The use of diazepam as an adjunct in obstetrical analgesia. In preparation.

Gerrard, J. W.: Kernicterus. *Brain 75: 526–570 (Dec) 1952.*

Gesell, A., and Amatruda, C. S.: *The Embryology of Behavior,* New York: Harper & Bros., 1945.

Harris, R., and Tizard, J. P.: The electroencephalogram in neonatal convulsions. *J Pediat 57: 501–520 (Oct) 1960.*

Hill, R. M., Desmond, M. M., and Kay, J. L.: Extrapyramidal dysfunction in an infant of a schizophrenic mother. *J Pediat 69: 589–595 (Oct) 1966.*

Koenigsberger, M. R.: Judgment of fetal age. I. Neurologic evaluation. *Pediat Clin N Amer 13: 823–833 (Aug) 1966.*

Paine, R .S.: Neurologic examination of infants and children. *Pediat Clin N Amer 7: 471–510 (Aug) 1960.*

PEIPER, A.: *Cerebral Function in Infancy and Childhood,* New York: Consultant's Bureau, 1963.

PRICHARD, J. S.: "The character and significance of epileptic seizures in infancy," in Kellaway, P., and Petersen, I. (eds.) : *Neurological and Electroencephalographic Correlative Studies in Infancy,* New York: Grune & Stratton 1964.

ROBINSON, R. J.: Assessment of gestational age by neurologic examination. *Arch Dis Child 41: 437–447 (Aug) 1966.*

RUDOLPH, A. J., DESMOND, M. M., and PINEDA, R. G.: Clinical diagnosis of respiratory difficulty in the newborn. *Pediat Clin N Amer 13: 669–692 (Aug) 1966.*

SCHWARTZ, J. F.: Neonatal convulsions. Pathogenesis, diagnostic evaluation, treatment, and prognosis. *Clin Pediat 4: 595–604 (Oct) 1965.*

SCHWARTZ, P.: *Birth Injuries of the Newborn,* New York: Hafner Publishing Co., 1961.

SMITH, C. A.: The professor, the student, and the newborn infant. *Univ Mich Med Bull 25: 293–304 (Aug) 1959.*

VAN PRAAGH, R.: Causes of death in infants with hemolytic disease of the newborn (erythroblastosis fetalis). *Pediatrics 28: 223–233 (Aug) 1961.*

EEG IN PREMATURES AND SUBSEQUENT DEVELOPMENT*

RUDOLF ENGEL, M.D.
Department of Pediatrics
University of Oregon Medical School
Portland, Oregon

It is a great challenge to determine neonates' state of development and to evaluate their functional maturation. Birthweight alone is misleading in 50 percent of small neonates. While neurologic maturation pattern can be related to conceptional age, the latter remains vague in individual cases. On the other hand, Dreyfus-Brisac and Samson-Dollfus estimated gestational age from EEG patterns with a margin of error of about two weeks.

EEG Patterns in Premature Infants

My own observations have yielded the following typical data:

In one nonviable fetus of 19 weeks gestation, a basic occipital frequency of 9 Hz to 10 Hz was recorded (fig. 1). This EEG cannot be classified as normal, since the heart rate already was abnormally slow. When the pulse rate dropped below 30 beats/min., the tracing became isoelectric.

At 7 months conceptional age, EEG activity varies between 0.5 Hz and 16 Hz, with bursts of 4 Hz to 6 Hz and 8 Hz to 16 Hz spreading from the occipital areas. This changes to rolling slow waves of about 1 Hz with low voltage 12–20 Hz ripples superimposed. Synchrony between the hemispheres is poor. Differentiation between waking and sleeping pattern becomes characteristic at 32 weeks, after which it is the most important feature (Dreyfus-Brisac).

The alternating tracing of deep sleep becomes evident at 8 months. A wide variety of frequencies, usually of moderately low voltage, appear in waking; wild bursts of greatly increased voltage interspersed with depressed phases are found during sleep. Scattered spikes or sharp waves are normal.

At 9 months, the alternating tracing can be obtained from all infants. Rudimentary spindles are the rule in full-term neonates, but a synchrony persists.

Evoked Photic Responses

Ellingson was the first to observe systematically the correlation between maturational changes in pattern and latency measurements of evoked responses in human neonates. We confirmed his observations in 2,000 newborns in Oregon.

---

*Supported by grant NB-02370, National Institutes of Health

245

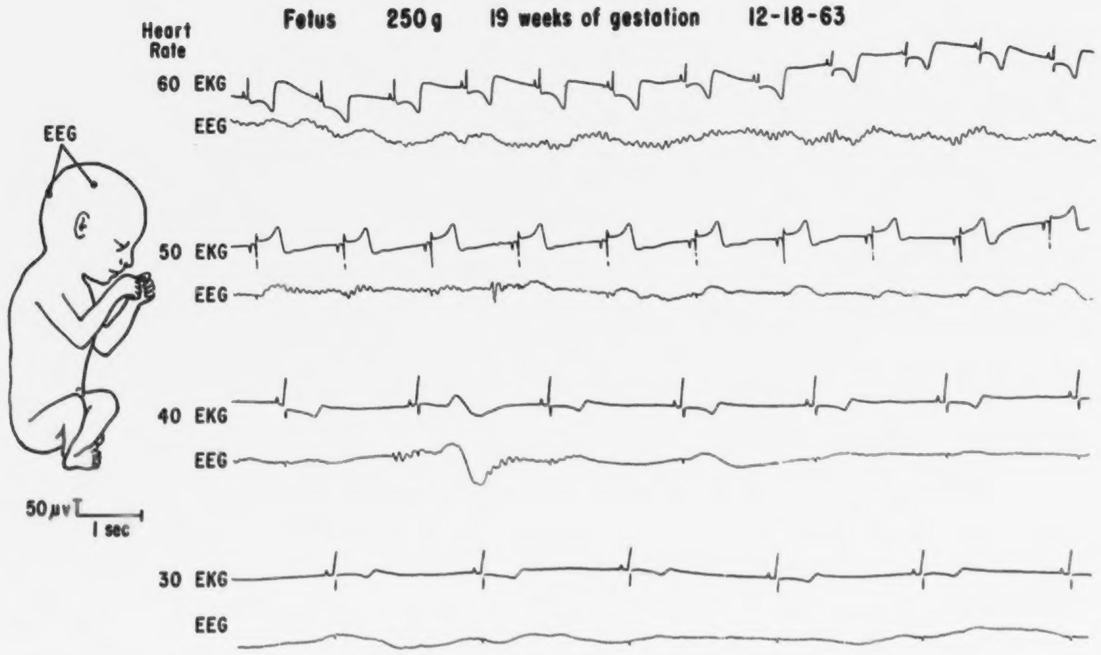


FIGURE 1.—EEG and electrocardiogram of a non-viable fetus, conceptional age 19 weeks.

"Latency" and "peak latency," estimated and measured by visual inspection of the ink record, are defined as the times from the stimulus to the points N_1 and P_2, respectively, in figure 2. The evoked response with its prolonged latency subsequent to flash is demonstrated in figure 3, along with the characteristic rolling slow waves and superimposed ripples.

In near-term and full-term neonates, the major evoked response wave over the inion is positive, though it may be surface-negative in early prematurity. It is preceded and followed by a sequence of waves that as a rule escape recognition on visual inspection. Using an adding computer, however, evoked photic response can be measured in all normal neonates.

Photic latency is inversely related to conceptional age in the neonatal period (fig. 4). Sex and race play a minor but significant role at term, girls showing a faster response than boys and Negroes reacting slightly faster in each subgroup. Children born in multiple births, many of them premature, showed a tendency to lag behind (fig. 5). Weight was not a decisive factor, nor was order of birth in twins. When measured at 40 weeks conceptional age, some prematures showed a slower response activity than did their contemporaries who matured in utero.

The considerable standard deviation of ±20 msec (about 10 percent) is the result of individual differences. Some of these differences can be correlated with race and sex; but within each racial and sexual group, the standard deviations are about as large as that in the entire sample.

Photic Latency and Other Maturational Measures

The prospective NIH Collaborative Project on Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Child-

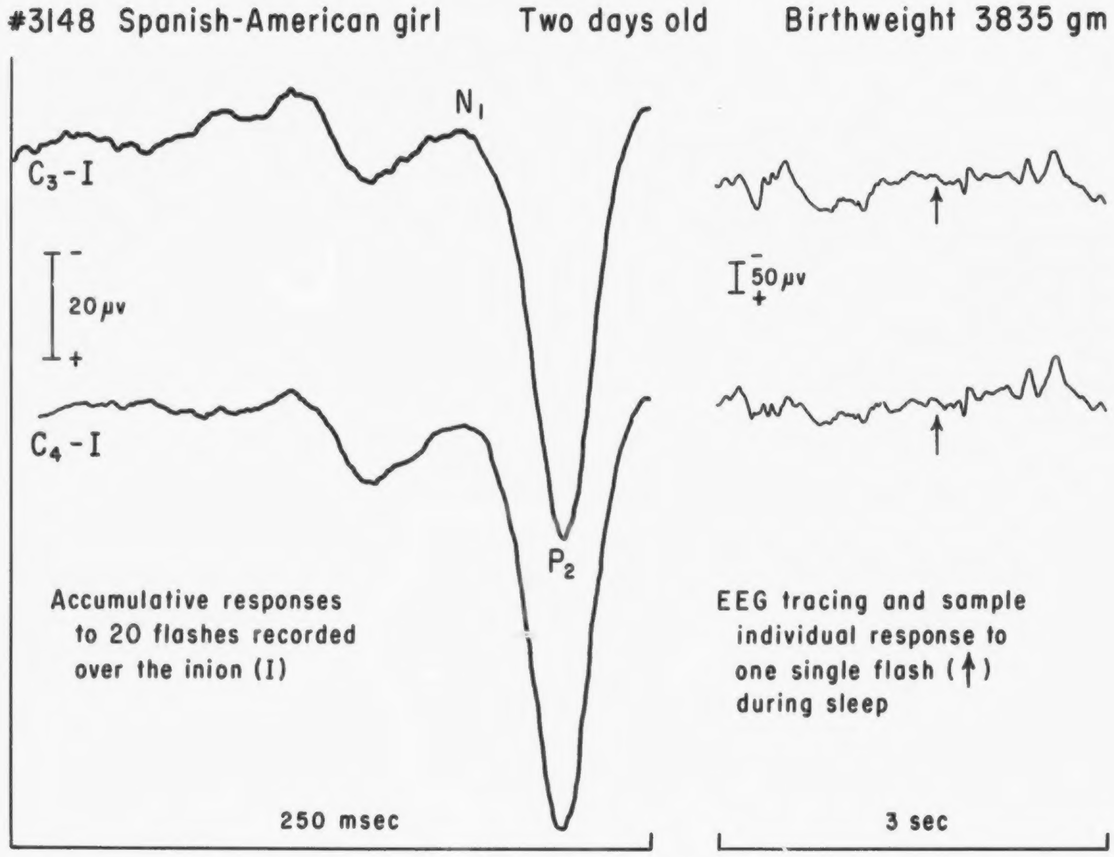


FIGURE 2.—Accumulative (left) and single (right) evoked responses recorded with scalp electrodes during neonatal period.

hood presented an opportunity to assess the relationship between neonatal photic latency and other measures of maturity. Participants in the project are offered psychological evaluation at 8 months and a pediatric-neurologic examination at 1 year. The analysis of the 8-month examination was carried out by B.V. Butler, Ph.D.

Eighth-month performance was measured by a modified version of Bayley's developmental scales. The 433 infants in our study were rated in three separate areas: (1) Mental-responsiveness to objects, vocalization, etc.; (2) Gross motor-sitting, stepping, pulling up; and (3) Fine motor-hand and finger dexterity. Scores in all three areas were adjusted for differences in age at the time of testing. In addition to photic latency two other neonatal measures—birthweight and gestational age—were compared with these 8-month ratings.

Table 1 shows that the relationship between neonatal photic latency compares favorably with gestational age as a predictive measure. The degree of correlation in all areas is noticeably greater for photic latency than for birthweight.

A different approach was taken when the neonatal measurements were related to performance at the 12-month neurologic examination. The 1,074 children tested were grouped according to neonatal latency measurements into three classes: (1) fast reactors, with latencies of 145 msec or less; (2) average, whose latencies were between 146 msec and 175 msec; and (3) slow reactors, with laten-

TABLE 1.—*Pearson relationships between three physiological neonatal variables and three measures of 8-month development* (N–433).

8-month scores	Neonatal Photic latency	 Gestational age	 Birth weight
Mental	−.33***	.31***	.18***
Fine Motor	−.24***	.26***	.15**
Gross Motor	−.23***	.23***	.12**

*.05 significance level
**.01 significance level
***.001 significance level

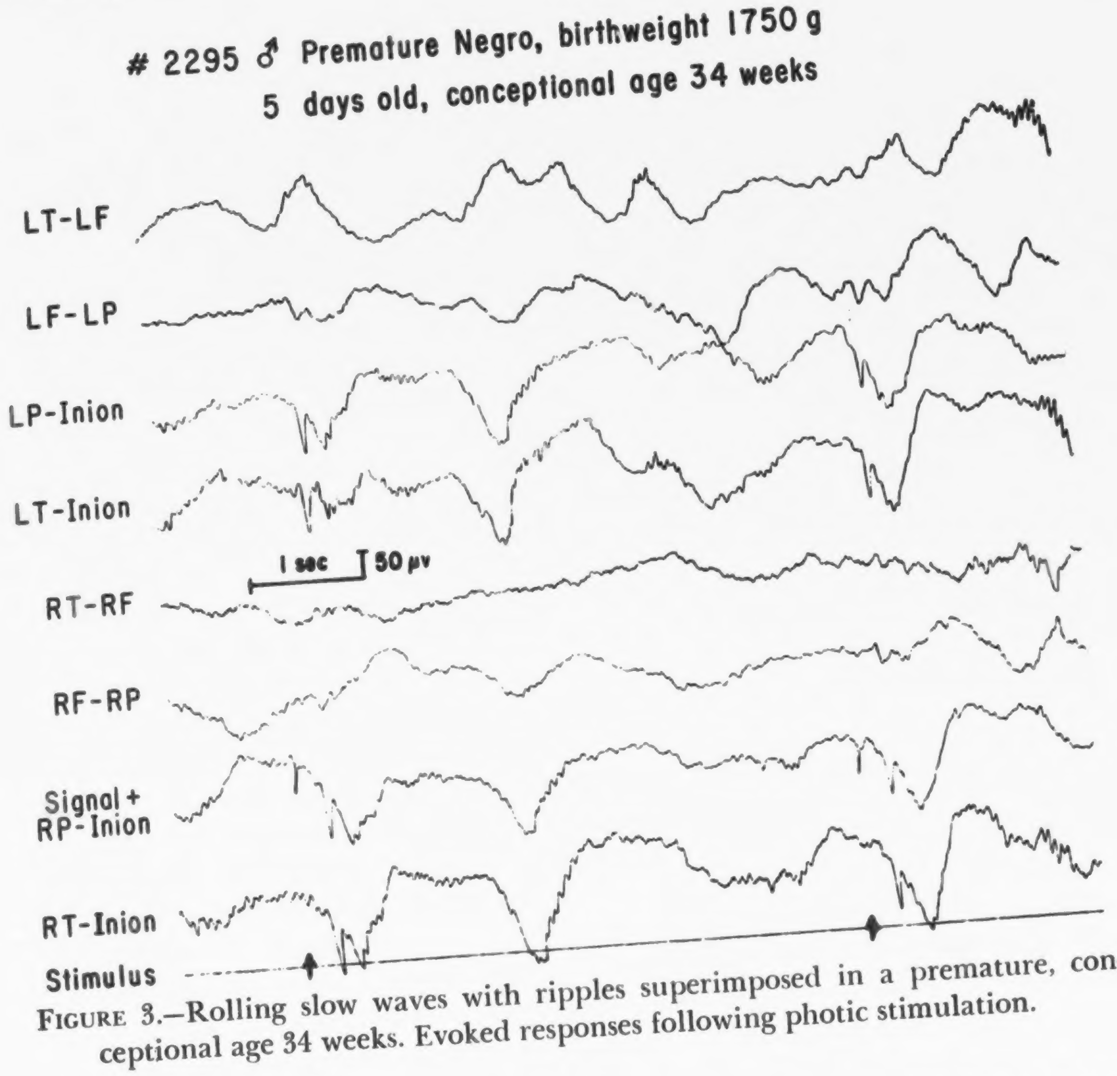


FIGURE 3.—Rolling slow waves with ripples superimposed in a premature, conceptional age 34 weeks. Evoked responses following photic stimulation.

cies greater than or equal to 175 msec. The third group contained many prematures.

We then tested whether the children were able to walk, unsupported. Only the neurologist's observation was accepted, and no attempt was made to grade the walking ability. No measurements of children with abnormalities were included. While some of the children came in on their birthdays, others were brought in a

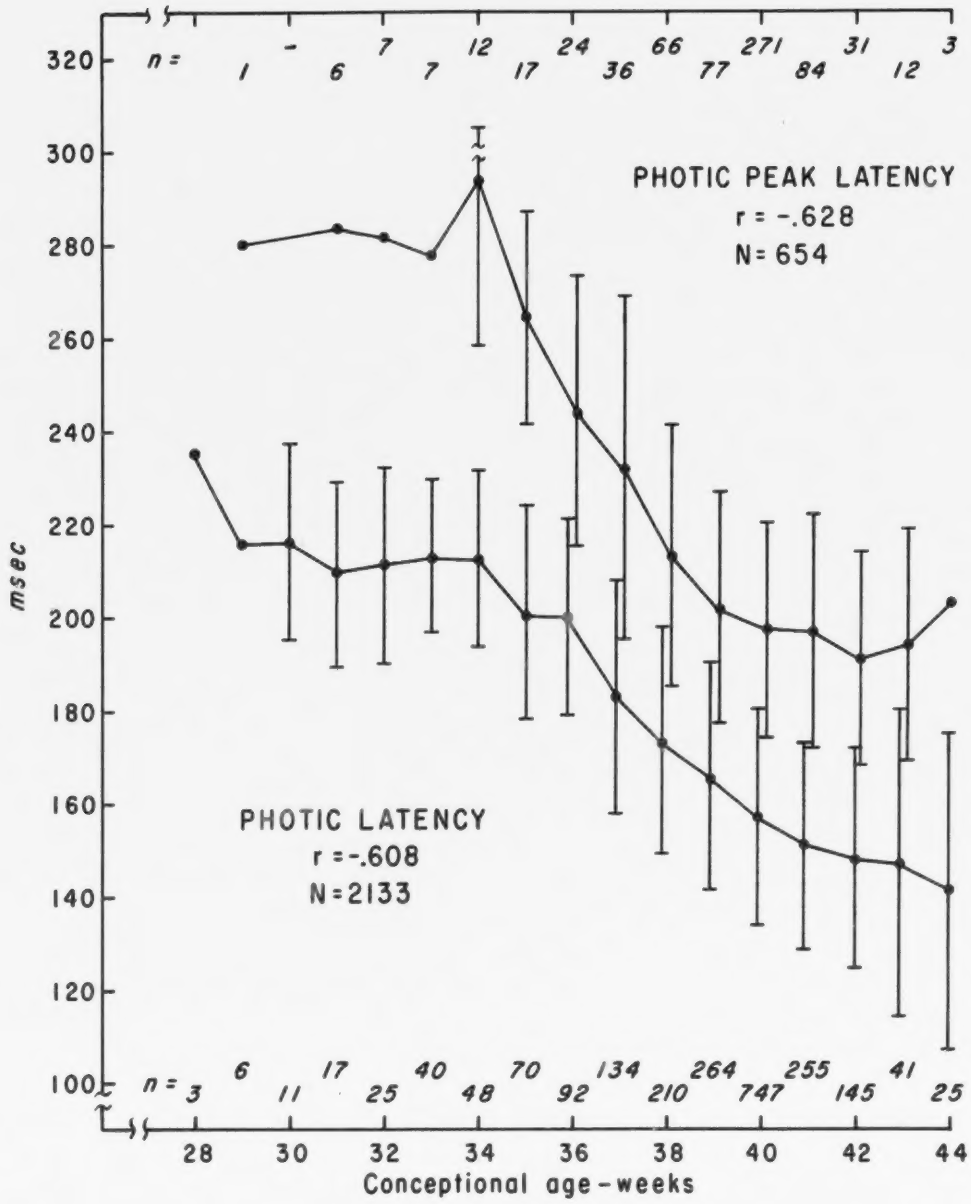
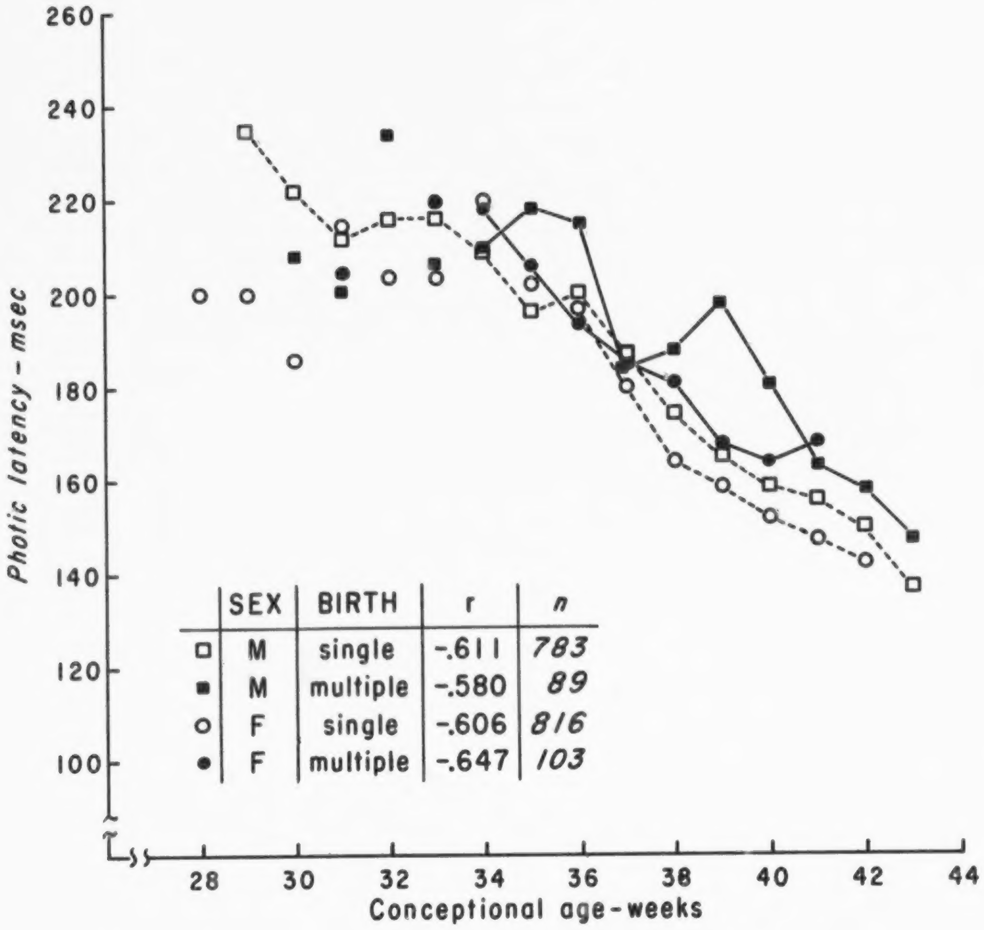


FIGURE 4.—Relationship and standard deviation of mean latency and of mean peak latency of photic response and conceptional age at time of EEG during the neonatal period. n = number of observations at each conceptional age by weeks. N = number of total observations, r = correlation coefficient.

couple of weeks earlier, and some needed repeated invitations and were therefore tested late.

In contrast to prematures, whose conceptional age is less at their first anniversary, a higher percentage of the latecomers could walk without support. In figure 6 the percentage of free walkers is plotted according to conceptional age at the time of observation. At 87 weeks of conceptional age less than 25 percent of the children were able to walk alone; at 98 weeks the figure reached 75 percent. But within each conceptional-age group the children who had been fast reactors



	SEX	BIRTH	r	n
□	M	single	-.611	783
■	M	multiple	-.580	89
○	F	single	-.606	816
●	F	multiple	-.647	103

FIGURE 5.—Mean photic latencies of single and multiple births plotted against conceptional age. M = male; F = female neonates.

at birth showed a higher percentage of early walkers and, with one exception, there were fewer free walkers among the slow reactors at birth.

The statistical analysis of significance presented a problem: how to handle a sequence of events on a gliding time scale? The solution was found by Donald Jensen, Ph.D., Associate Professor of Statistics, Virginia Polytechnic Institute. The analysis of variance for comparing percent walking in the three photic latency groups showed a significant F value of 8.8049 (Table 2).

TABLE 2.—*Analysis of variance for comparing percent walking in three photic latency groups*

Source	d.f.	S.S.	M.S.	F
Residual from Common Line	28	6.321953		
Pooled Residuals from separate lines	24	2.562102	.106754	
Difference	4	3.759851	.939963	8.8049

The problem would appear at this point to be a standard regression problem . . . it is not. The dependent variable, expressed either in percents or as a fraction, is binomial. Further, the group sizes are different as indicated at the top of figure 6. For both of these reasons, weighted linear estimation is required and the problem is further complicated by the fact that the correct weights are not known. To circumvent this difficulty, Dr. Jensen developed a program which used an iterative procedure involving estimated weights. First the lines were estimated using one set of weights, then new weights were obtained from the estimated line, and the procedure was continued until the estimated parameters of the linear models agreed to four decimal places. Several iterations were required for each problem, the number ranging from 5 to 13 in the data. When the weighted regression analysis using the arcsine (in radians) of the square root of the fraction of walkers in each group was completed, there was no significant departure from linearity. The evidence strongly suggests that the trends observed in the chart are significant and thus the percent walkers at a given age correlates with the neonatal photic latency grouping for the range of ages studied.

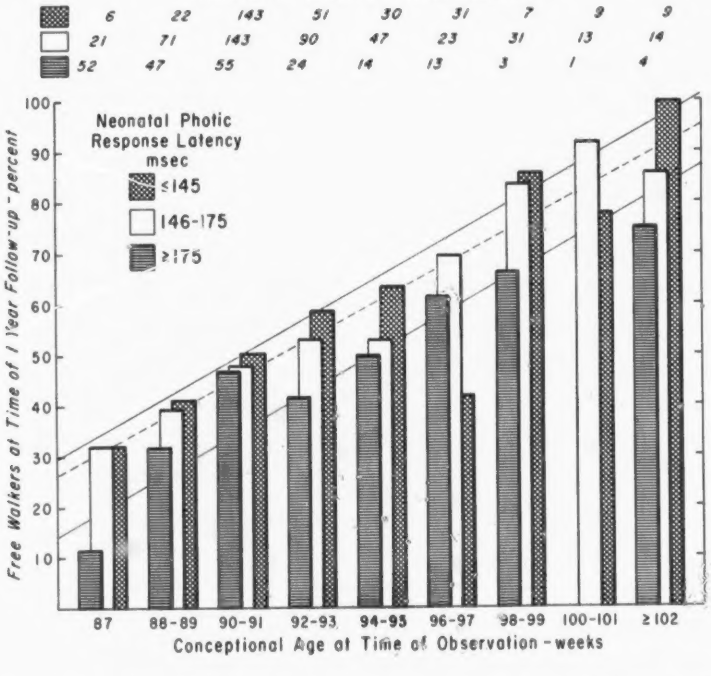


FIGURE 6.—Percentage of free walkers in 3 groups of children distinguished by fast, medium or slow evoked responses as neonates and tested one year later for their ability to walk unsupported. The 3 groups of 1-year olds are subdivided according to conceptional age at time of testing in increments of 2 weeks.

In contrast to locomotion, phonation at one year of age (intelligible words during the period of observation by the physician) did not correlate with the neonatal response latency measurements.

Diagnostic Value of the EEG in Prematures

At least one abnormal tracing was found in 10 percent of EEG's of 564 prematures (Table 3).

TABLE 3.—*Incidence of neonatal EEG abnormality among 564 prematures with clinical follow-up of one to seven years later. (On-going study)*

Neonatal EEG Pattern	Leading EEG abnormalities	Number	Normal at follow-up	Died	Cerebral palsy	Mental retardation	Arrested hydrocephalus	Neurologically suspect	Congenital abnormalities	Rubella syndrome	No follow-up
	Focal or multifocal spikes	26	15	1	2	—	2	3	3	—	—
	Burst suppression or paroxysmal pattern	12	—	—	5	2	1	—	—	1	3
	Depression of electrical activity	15	—	5	1	3	—	2	—	—	4

The main categories of EEG abnormality are:

(1) Focal or multifocal spikes
(2) Burst suppression or paroxsymal pattern
(3) Diffuse or hemispheric depression of electrical activity

Ten percent represents a greater proportion of abnormal EEG's than would be expected in a prospective study of full-term neonates. High-risk cases, of course, are accumulated in a special-care unit for prematures.

The clinical follow-up employs the classification of the longitudinal study of Torres and Blaw on Collaborative Project children in Minnesota. Over half the children in Group 1 were clinically normal. Focal spikes in prematures do not necessarily seem to be an abnormal finding; even if they occur frequently, they are entirely reversible. The highest incidence of cerebral palsy was found in Group 2; no proven normal child was in this group.

Children in Group 3, severe electrical depression, had the most ominous prognosis. One-third of these children died, and another fifth were mentally retarded. One hydranencephalic premature infant is included in this series.

The follow-up periods in this on-going study are still uneven, between 1 and 7 years. A statistical analysis with controls is not yet available. A number of children who later proved to have cerebral palsy had no definite abnormality in their original neonatal record. The subject of abnormal neonatal EEG's could not be ignored in the discussion of the EEG in prematures and subsequent development. The question of the prognostic value of a definitely abnormal EEG tracing or its absence in the neonatal period is still wide open.

DISCUSSION

DOCTOR HON: Did any of these prematures with abnormal EEG's subsequently develop seizures? Secondly, I think you said you had one patient with hydrancephaly in the series. I was curious to know if there was an evoked potential response in that individual?

Doctor Engel: If I may answer this last question first, this baby just fascinated me. All the cranial nerves were perfectly intact, but there were no evoked responses either to photo or to acoustic stimulation. We did a postmortem study and could prove that the cranial nerves all were intact. There are some who develop seizures, but I cannot tell you the percentage.

Doctor Decker: I have done a great deal of this premature EEG work over the last 6 or 7 years. We have about 850 records all done on prematures starting with early 6 month's gestation and following through with neurological exams until 2 or 3 years of age, done by myself. With experience, I have found that I can estimate gestational age within a week of these infants, proved by their maternal records. However, we have been very disappointed by our failure to predict neurologic damage from the EEG's and the neurologic examinations which were done in the nursery. We have had babies who have had abnormal EEG's who then became perfectly normal, and we have had depressed hemispheric records that the next time were perfectly normal. We have had children who looked good up until 8 years of age, and then showed abnormalities. We had one child whose mother was toxemic, who showed an abnormal record in the premature nursery and rapidly, very rapidly after his discharge, showed the classic signs of hypsarrhythmia with gross neurological deficit.

We have had, I would estimate, about 8 percent abnormals in this group of children.

REFERENCES

Bayley, N.: *California First-Year Mental Scale.* Berkeley: University of California Press, 1933.

Butler, B. V., and Engel, R.: Mental and motor scores at 8 months in relation to neonatal photic responses. Annual meeting of the American Academy of Cerebral Palsy, December 1967.

Dreyfus-Brisac, C., Fischgold, H., Samson-Dollfus, D., Sainte-Anne Dargassies, S., Monod, M., and Blanc, C.: Veille, sommeil, reactivité sensorielle chez le prematuré, le nouveauné et le nourrisson. *Electroenceph Clin Neurophysiol* (*Suppl 6*) : *417–440, 1957.*

Dreyfus-Brisac, C.: The electroencephalogram of the premature infant and full term newborn. *Neurological and Electroencephalographic Correlative Studies in Infancy,* (ed.) , P. Kellaway and I. Peterson, New York: Grune & Stratton, 1964, pp 186–207.

Dumermuth, G.: *Elektroencephalographie im Kindesalter.* Stuttgart: Thieme Publishing, 1965.

Ellingson, R. J.: Cerebral electrical responses to auditory and visual stimuli in the infant. *Neurological and Electroencephalographic Correlative Studies in Infancy.* (ed.) , P. Kellaway and I. Peterson, New York: Grune & Stratton, 1964, pp 78–115.

Ellingson, R. J.: Studies of the electrical activity of the developing human brain. *Progress in Brain Research,* (ed) W. and H. Himwich, New York: Elsevier, 1964 pp 26–53.

Engel, R., and Butler, B. V.: Appraisal of conceptional age of newborn infants by electroencephalographic methods. *J Pediat 63: 386–393* (*Sept*) *1963.*

Engel, R.: Maturational changes and abnormalities in the newborn electroencephalogram. *Develop Med Child Neurol 7: 498–506* (*Oct*) *1965.*

Engel, R., and Benson, R. C.: Estimate of conceptional age by evoked response activity. *Biol Neonat 12: 201–213, 1968.*

Janzen, R., Schroeder, C., and Hecke, H.: Hirnbioelektrische Befunde bei Neugeborenen. *Mschr Kinderheilk: 100: 216–218* (*Apr*) *1952.*

Janzen, R., Bushart, W., Engel, R.: Zur aussagekraft des EEG beim neugeborenen, Katamnestische untersuchungen. *Deutsch Z Wervenheilk 193: 245–255, 1968.*

KELLAWAY, P., and CRAWLEY, J.: A primer of electroencephalography of infants. *Methodology and Criteria of Normality:* Baylor University College of Medicine, 1964.

TORRES, F., and BLAW, M. E.: Longitudinal EEG—clinical correlations in children from birth to 4 years of age. *Pediatrics 41: 945–954 (May) 1968*

HEMATOLOGIC FACTORS IN THE PREMATURE INFANT AND MENTAL RETARDATION

Frank A. Oski, M.D.
Department of Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Although no attempts have been made to relate disturbances in the newborn's coagulation mechanism to subsequent mental retardation, existing evidence suggests that the premature infant is more susceptible to hemorrhage after trauma.

The coagulation mechanism consists of two complementary processes. As a response to bleeding, the platelets aggregate into a plug to patch the vessel defect. This plug is then strengthened and reinforced through a process involving the interaction of 13 factors that act in a cascade fashion of linked reactions to result in the eventual generation of fibrin. The thrombin generated in the classic second stage of coagulation causes the loose platelet plug to contract and fuse into a stronger and longer-lasting plug. Thrombin also acts to convert fibrinogen to fibrin, which becomes a matrix that entraps red and white cells and causes extension of this platelet plug.

Abnormal bleeding, therefore, may be the result of irregularities in vessels, platelets, or coagulation factors. Examination of these areas in the premature infant reveals abnormalities in each.

As early as 1924, Ylppö demonstrated that the capillaries of the premature infant were unusually fragile. In infants weighing less than 1,000 gm a negative pressure of 150 mm Hg uniformly produced capillary rupture and eccymosis. Infants weighing 1,500 gm to 2,000 gm or more could tolerate 520 mm Hg of negative pressure. These studies have been confirmed, but no attempt has been made to relate them to the presence of cerebral hemorrhage.

Some premature infants also exhibit marked reductions in their platelet counts. In general, however, this thrombocytopenia has not been associated with bleeding. In addition, Hilgartner has recently reported that platelet function also is frequently abnormal during the first day of life. This is reflected in poor clot retraction, abnormal platelet factor III release, and impaired aggregation of platelets after incubation with adenosine diphosphate. In the term infant this functional thrombasthenia disappears during the first few days of life. Its duration has not been studied in the premature infant.

Some premature infants demonstrate marked alterations in the coagulation mechanism as well, particularly in the generation of thromboplastin and thrombin. In the premature infant, the levels of prothrombin and of factors VII, IX, and X may be low and often do not reach normal with vitamin K administration. This failure to respond has been interpreted as a reflection of liver immaturity and consequent inability to synthesize these factors.

The question is whether these infants are at risk. In a study of newborns, Gray and Smith employed the Thrombotest, a simple one-reagent test devised by Owren. This test measures prothrombin and factor VII, IX, and X activity and requires only 0.05 cc of blood from a heel prick. Of 32 infants judged to be clinically normal, only two had Thrombotest values less than 10 percent. Of 42 premature infants considered ill, 12 had values less than 10 percent. Eight of these infants died. Seven of them had Thrombotest values less than 10 percent on the first day of life, and three had massive cerebral hemorrhage at the time of death. The authors conclude that the danger arises when, in addition to minor cerebral damage such as may occur during the birth process, there is also a marked clotting defect.

The importance of other factors in the genesis of the bleeding is shown by the fact that few newborn infants hemorrhage solely because of congenitally defective coagulation mechanisms. Infants with classic hemophilia rarely bleed. Infants with severe neonatal thrombocytopenia do bleed, but it is serious in only about 15 percent of the cases. This suggests that the primary factors in the bleeding might be capillary fragility and impaired platelet function, or trauma could lead to anoxia, thereby causing abnormalities in the coagulation process.

Aballi and associates recently reported the results of their investigation of 32 newborns with intracranial hemorrhage, 27 of whom had low birth weight. In all but four the hemorrhage was fatal. Thrombocytopenia and altered capillary fragility were found in some, but the most important alterations were plasmatic. They consisted of a prolonged prothrombin time, an abnormal partial thromboplastin time, and a marked depression of factor V levels. These abnormalities did not respond to vitamin K administration. Since products of fibrinogen degradation were found, intravascular coagulation may have taken place. Consumption of coagulation factors during such accelerated coagulation could explain the abnormalities.

These so-called consumption coagulopathies are currently receiving much attention. Anoxia and shock are two factors that could initiate the process. If the process is recognized early enough, use of the anticoagulant heparin is the treatment of choice.

Much work obviously remains to be done to sort out the responsible factors in the hemorrhage of the newborn. Are increased capillary fragility and minimal birth trauma the main etiologic factors? Do these result from liver immaturity, or does birth trauma, anoxia, shock, or sepsis initiate disseminated intravascular coagulation with resultant depletion of coagulation factors and subsequent hemorrhage? Of those infants who hemorrhage, what percentage die, what percentage have residual impairment, and how many recover completely?

REFERENCES

ABALLÍ, A. J., AVELINA, M., COSTALES, F., and ACS, H. *Program of American Pediatric Society*, 1968, p. 28.

ABALLÍ, A. J., LÓPEZ-BANUS, V., DELAMERENS, S., and BORRAJERO, I. Trastornos hemorragicos en el prematuro. *Rev. Cubana Pediat. 28:* 651–686, Nov. 1956.

BERNFELD, W. Experimentelle Untersuchung en über die capillar resistenz junger, in sbesondere fruhge-borener säuglinge (Saugglocken Methode). *Mschr Kinderheilk 51:* 1–14, 1931.

FOGEL, B. J., ARIAS, D., and KUNG, F. Platelet counts in healthy premature infants. *J. Pediat. 73:* 108–110, July 1968.

GRAY, O. P., and SMITH, S. G. The thrombotest on first day of life. *Acta Paed. Scand. 55:* 563–568, Nov. 1966.

HILGARTNER, M. W. *Program Soc. Pediat. Res.*, 1968, p. 120.

MEDOFF, H. S. Platelet counts in premature infants. *J. Pediat. 64:* 287–289, Feb. 1964.

OZTALAY, A. G., BEARD, A. G., and PORTER, F. S. Thrombocytopenia in premature infants. *Lancet 86:* 133–135, March 1966.

ROGNER, G. Gerinnungsphysiologische thrombocyten untersuchungen bei reifen und unreifen neugeborenen in der ersten lebenswoche. *Z. Kinderheilk 88:* 1–10, 1963.

YLPPÖ, A. Zum Entstehungsmechanismus der blutungen bei frühgeburten und neugeborenen. *Z. Kinderheilk 38:* 32–45, 1924.

SESSION VI

Postnatal Trauma

Session Chairman: Charles Barlow, M.D.

POSTNATAL TRAUMA: SUBDURAL HEMATOMA

L. K. Page, M.D., A. D. Rosenthal, M.D.,
W. D. Morain, M.D., and J. Shillito, Jr, M.D.
Department of Neurosurgery
The Children's Hospital Medical Center
Boston, Massachusetts

The same therapeutic approach was used in subdural hematoma at the Children's Hospital Medical Center, Boston from 1937 to 1967. Initial diagnostic subdural taps were first made; then daily taps were made, removing 15 cc to 20 cc of fluid at a time for 5 to 7 days.

When the fluid persisted, burr holes were placed bilaterally. If no membranes were found on either side, the subdural spaces were irrigated with saline; postoperative taps were continued at intervals until the subdural spaces remained dry. If membranes were found on one side, a large frontotemperoparietal osteoplastic craniotomy flap was turned, and the outer and inner membranes were removed. If membranes were present bilaterally, one craniotomy was performed when the burr holes were made and the other 7 to 10 days later.

The peak incidence in this study of subdural hematomas in children below 1 year of age is at 6 months. This is a time of rapid growth and development for the brain. Subdural bleeding stimulates the growth of a membrane (fig. 1) from the inner surface of the dura that can be seen grossly after 7 to 10 days. A well-developed outer membrane several millimeters thick may be tough, inelastic, and highly vascular (fig. 2). The inner membrane between the hematoma and the arachnoid is usually quite thin and transparent; but it may offer resistance to the rapid brain growth and development that occur in early childhood (fig. 3). In neglected infants with subdural hematomas of long standing the membrane may be as thick and tough as the dura. These patients may show marked cerebral atrophy with an increase in the size of the ventricles as well as in the depth of the subarchnoid space.

Our approach has been to deal with the persistent hematomas directly by excising their membranes (Ingraham and Heyl; Ingraham and Matson) rather than by shunting the fluid to another body compartment (Ransohoff; Schulman and Ransohoff). In this follow-up study 120 cases of nonmeningitic subdural hematoma were treated at the Children's Hospital from 1949 to 1958 (Table 1). There was known trauma and/or skull fracture in 75 patients. A history of birth trauma was obtained 20 times. Preoperative convulsions were present in 43 patients; failure to thrive was a presenting complaint 32 times. Cranial enlargement was present in 20 patients and microcephaly in 3.

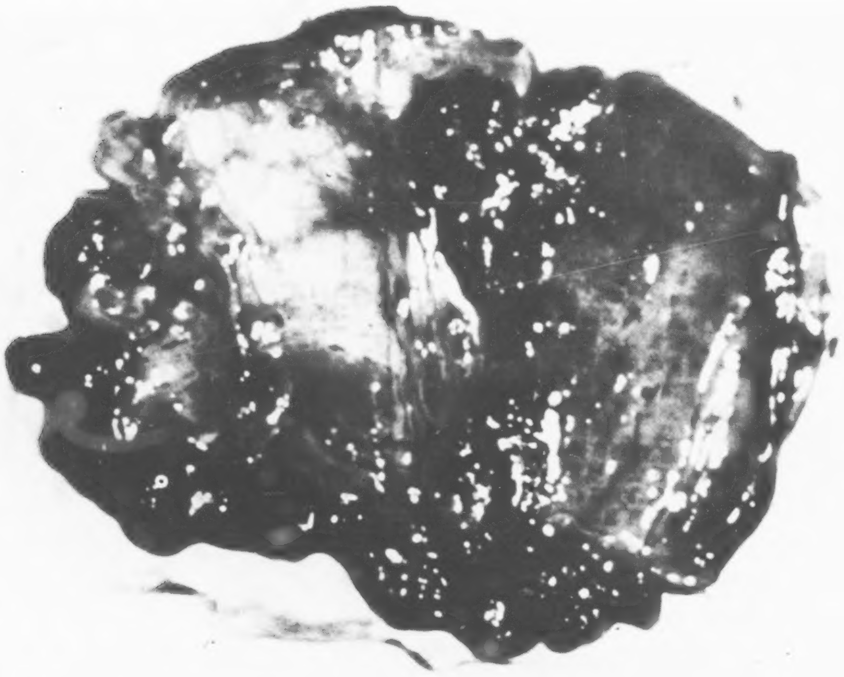


FIGURE 1—Outer membrane excised from an infant with subdural hematoma.

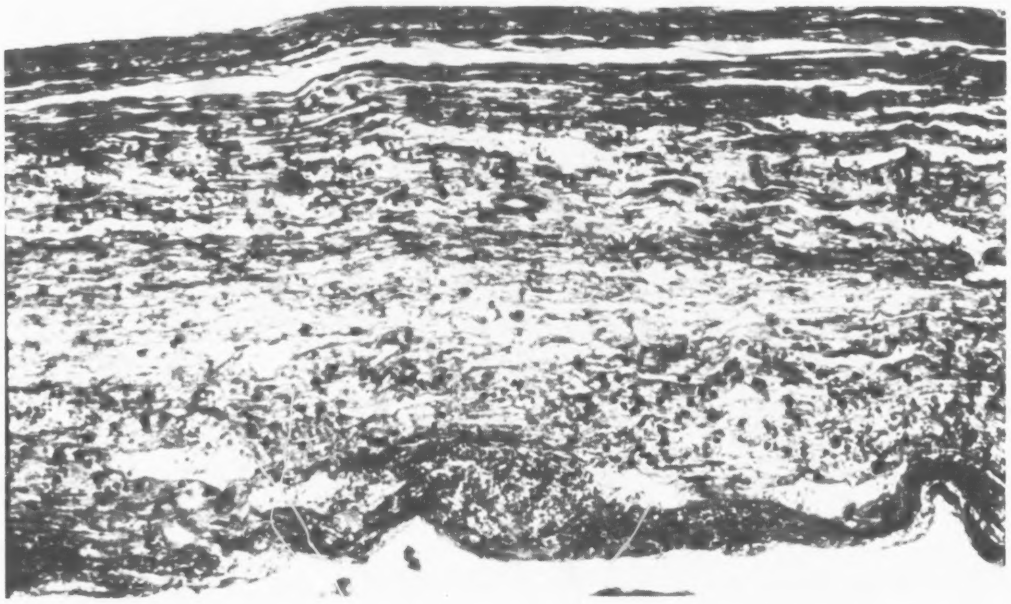


FIGURE 2—Well developed membrane. Note large collagen and vascular components.

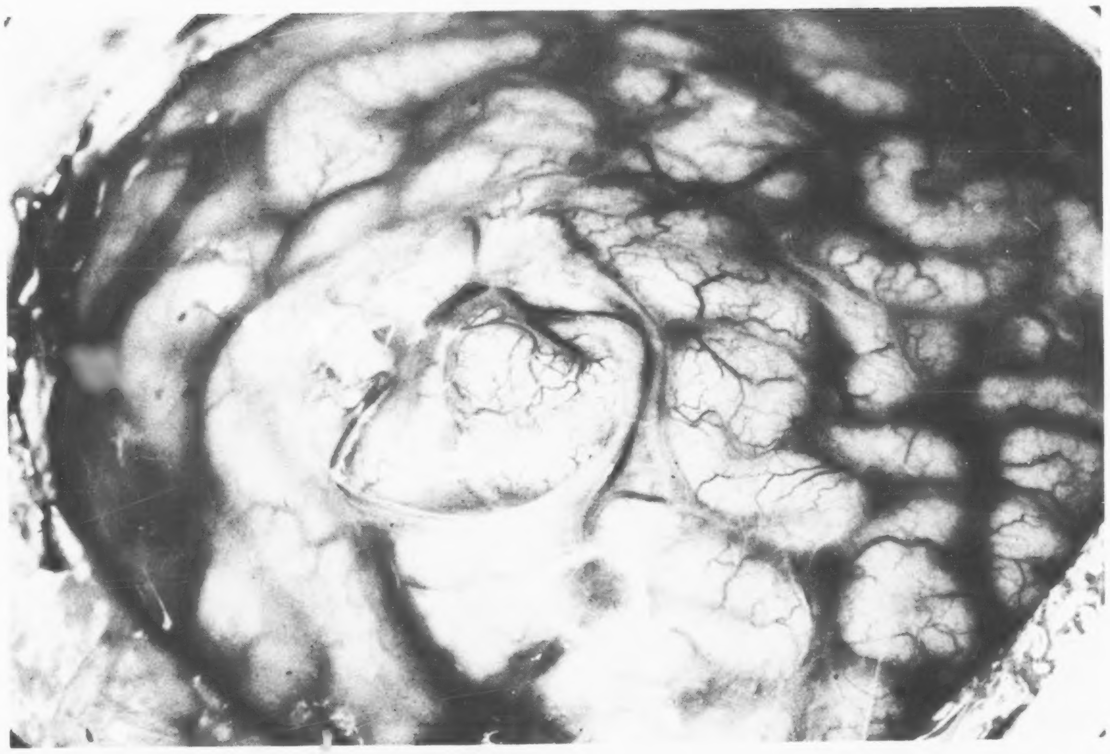


FIGURE 3—A small linear incision in this inner membrane has rapidly expanded to a circular defect as brain bulges through.

TABLE 1

Subdural Hematomas	120
Past History	
Trauma and/or Skull Fracture	75
"Birth Trauma"	20
Presenting Complaint	
Pre-operative Seizures	43
Failure to Thrive	32

Burr hole irrigations were used in 24 patients; 3 patients had subdural taps only (Table 2). Unilateral craniotomy was performed in 39 cases, and bilateral craniotomies for membrane excision in 54. Postoperative follow-ups for greater than 5 years were available in 86 patients. These are divided into 3 groups (Table 3). The first, the uneducable, comprised those who can do no more than care for themselves. Of the 25 in this group, 1 lived at home and 24 were institutionalized. Ten of the latter died in their institutions.

TABLE 2

Therapy	
Subdural Taps	3
Burr Holes	24
Unilateral Craniotomy	39
Bilateral Craniotomy	54

TABLE 3

Adequate Follow-Up (Greater Than 5 Years)
N=86

	N
1. Uneducable	25
2. Special Classes	10
3. Regular Classes	51

The second group, 10 children, were assumed to be educable and able to attend special classes. One died; 1 had seizures; 2 had marked motor deficits; and 4 had behavior problems.

The third group, 51 patients, attended regular classes. Three of these died of unrelated illnesses; 1 had a hemiparesis; 1 had a convulsive disorder; and 1 had a mild behavior problem.

Thus 59 percent of those followed for more than 5 years did well. The outcome was not clearly related to the degree of membrane formation (Table 4), but atrophy at the time of surgery was significantly related to subsequent retardation.

TABLE 4

	Membranes				
	N	*Absent*	*Filmy*	*Usual*	*Thick*
Uneducable	24	1	3	10	10
Regular	44	9	7	20	8

TABLE 5

	Brain			
	N	*Normal*	*Atrophy*	*Marked Atrophy*
Uneducable	19	8	10	1
Regular Classes	39	26	8	5

REFERENCES

COLLINS, W. F. and PUCCI, G. L.: Peritoneal drainage of subdural hematomas in infants. *J Pediat 58: 482–485, 1961.*

INGRAHAM, F. D. and HEYL, H. L.: Subdural hematoma in infancy and childhood. *JAMA 112: 198–204 (Jan 21) 1939.*

INGRAHAM, F. D. and MATSON, D. D.: Subdural hematoma in infancy. *J Pediat 24: 1–37 (Jan) 1944.*

LEARY, T.: Subdural hematomas. *JAMA 103: 897, 1934.*

MOISE, P. D., THOMPSON, G. B., GUFF, J. W.: Subdural peritoneal shunts in the treatment of subdural infusion in infants. *J Neurosurg 23: 584–587, 1965.*

PEET, M. M. and KAHN, E. A.: Subdural hematoma in infants. *JAMA 98: 1851, 1932.*

RANSOHOFF, J.: Chronic subdural hematoma treated by subdural pleural shunt. *Pediatrics 20: 561–564 (Sept) 1957.*

SHULMAN, K. and RANSOHOFF, J.: Subdural hematoma in children. The fate of children with retained membranes. *J Neurosurg 18: 175–181 (Mar) 1961.*

DEFINITION AND ETIOLOGY OF SUBDURAL HEMATOMA IN INFANTS AND CHILDREN

Edward F. Rabe, M.D.
Department of Pediatrics
Tufts University School of Medicine
Department of Pediatric Neurology
New England Medical Center Hospitals
Boston, Massachusetts

Although it is common to refer to blood-containing subdural collections of fluid as subdural hematomas and to presume that these collections were preceded by trauma, this sequence is not necssarily true.

Infants and children with subdural fluid containing from 23 to 350,000 rbc/mm^3 and a protein content of 88 to 4,300 mg% may have as their antecedent event head trauma, bacterial meningitis, pneumoencephalography, or diarrhea, dehydration, and convulsions. In addition, a significant number of such young patients may have no recognizable antecedent event, i.e., no circumstances that, in our present state of knowledge, could "cause" the subdural collections of fluid. Since children with subdural fluid, from whatever cause, may survive with chronic neurologic sequelae, it becomes important to examine the cause of such collections of fluid, define the importance of antecedent events in relation to prognosis, and discuss briefly the problems of management in the context of such information. This is done in the hope of clarifying the problem and aiming to improve the prognosis.

Bleeding from bridging veins into the subdural space is known to follow head trauma. Blood in the subdural space leads to an effusion of fluid from the dural capillaries as well as proliferation of the dural fibroblasts and vascular spaces contained in them. As time passes, the subdural fluid is composed of a decreasing population of red cells with a persistent fluid high in albumin. Eventually the fluid may disappear and the proliferated dura may atrophy. This describes the evolution of a subdural hematoma to an effusion and its final disappearance.

In addition to trauma, subdural bleeding may result from pneumoencephalography, dehydration with a constricted brain volume, or surgical approach to the brain. Subdural effusions can follow each of these antecedent events. On the other hand, the cause of subdural collections of fluid following meningitis is not clear.

Biopsy of the subdural membrane from patients with subacute or chronic collections of fluid following any antecedent event reveals a similar microscopic picture. Despite this similarity, the prognosis is varied, and the outcome is significantly affected only by the antecedent events. This conclusion is illustrated in Table 1.

TABLE 1.—*Outcome in 97 infants and children with subdural fluid according to antecedent event*

Antecedent Event	Total No.	Outcome Good	Outcome Fair-Poor	Outcome Dead
POST-INFECTIOUS	44	33[76]	10[22]	1[2]
POST-TRAUMATIC	20	9[45]	9[45]	2[10]
IDIOPATHIC	27	10[37]	12[44]	5[19]
MISCELLANEOUS	6	1[17]	3[50]	2[33]
Total	97	53[55]	34[35]	10[10]

KEY: NUMBERS IN BRACKETS INDICATE THE PERCENT OF THE TOTAL CASES
GOOD: (NORMAL). FAIR: (NEUROLOGICAL DEFICIT BUT CAN FUNCTION INDEPENDENTLY). POOR: (NEUROLOGICAL DEFICIT, CANNOT FUNCTION INDEPENDENTLY).

The data is derived from examining 87 surviving patients from 5 months to 11 years after hospital discharge, the average interval being three years. The difference in outcome between the postinfectious group and each of the others is statistically significant for each paired comparison: (P values - post-traumatic = 0.042; idiopathic = 0.010; miscellaneous = 0.010.)

Other factors have been considered important in determining the outcome of these patients. Chief among them is the subdural fluid itself. In patients with bleeding into the subdural space from broken bridging veins, and in patients with bacterial meningitis (initially with sterile fluid containing a high polymorphonuclear count), the envolving subdural effusion becomes xanthochromic and has an elevated protein and albumin content. Gitlen first noted that the albumin-to-globulin ratio in subdural effusions was greater than that in the serum obtained at the same time. This led to the assumption that the subdural effusions resulted from a transudation of fluid high in albumin through a vascular abnormality in the walls of the subdural membrane. This aberrant A/G ratio was found in all effusions, no matter what the antecedent event.

We have studied a number of infants with subdural effusions using iodine-131- labeled human serum albumin injected either intravenously or subdurally. Six infants ranging in age from 2 to 9 months were studied. Labeled albumin given intravenously appeared in the subdural space; the results indicated that subdural as well as subarachnoid albumin was derived from plasma. Subdurally injected labeled albumin appeared also in the plasma. These observations, together with the slopes of the curves of albumin-specific activity in each compartment, indicated a constant turnover of albumin between plasma and subdural space. In each infant the concentration of the labeled albumin in fluid from each of the spaces was different, indicating that plasma, subdural space, and subarachnoid space were not communicating directly with each other (figs. 1 and 2).

204

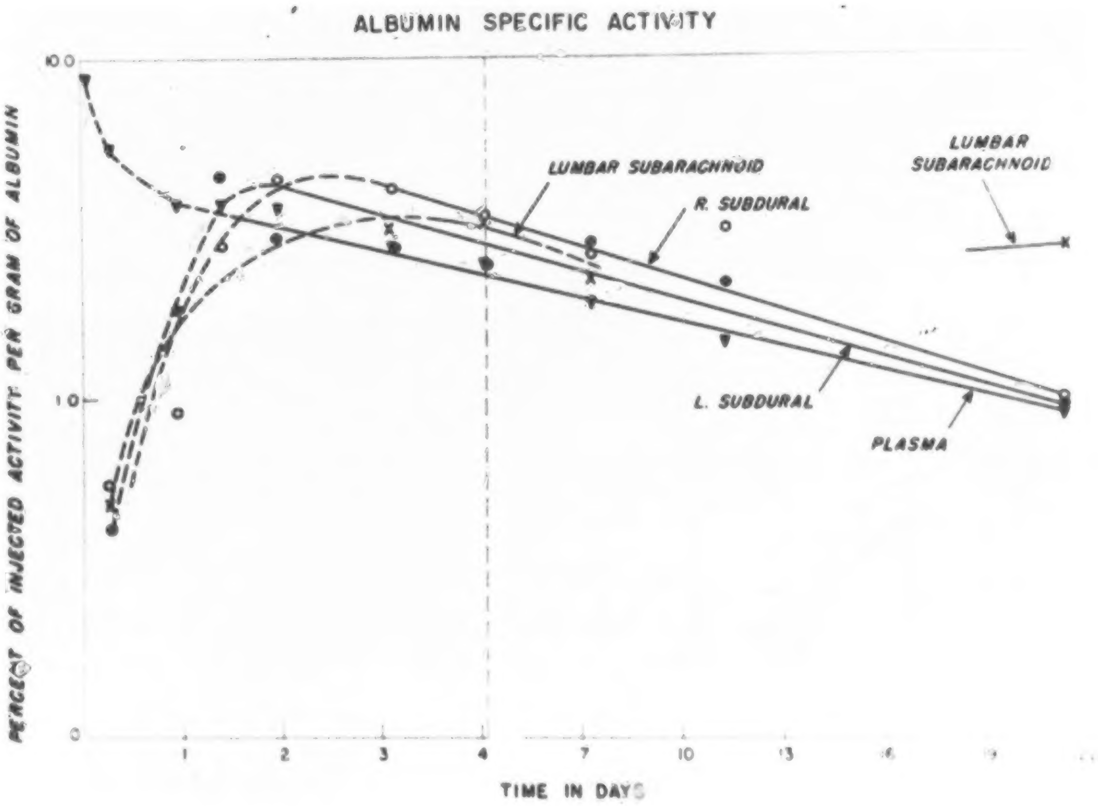


FIGURE 1—Albumin-specific activity in various fluids following the intravenous injection of 15μc of I^{131} RISA in a 5-month-old infant with post-traumatic subdural effusions

The duration of the effusion—measured by the time between the occurrence of the presumed antecedent event and the last subdural tap-yielding fluid—was compared with the measured albumin turnover time, turnover rate, and turnover as shown in Table 2. These terms are respectively the time it takes to turn over an

TABLE 2.—*Comparison of subdural albumin exchange with estimated duration of subdural effusions in four infants with subdural effusions*

Pt.	Age (Mos.)	Antecedent Event	Duration of Effusion (Days)	Albumin In Subdural Effusion: Turnover Time* (Hrs)	Turnover Rate* (mg/24 hrs)	Turnover % of Pool /24 hrs)*
D.C.	6.5	CONGENITAL ENCEPHALOPATHY	90	136.3	438	16
R.M.	3.5	TRAUMA	60	42.8	484	56
C.B.	2.5	MENINGITIS	20	23.6	596	102
J.M.	9.5	PNEUMOENCEPHALOGRAM	18	13.1	343	183

KEY* —TURNOVER TIME – TIME TO EXCHANGE AN AMOUNT OF ALBUMIN EQUIVALENT TO THAT IN SPACE; TURNOVER RATE – RATE OF ALBUMIN TURNOVER; TURNOVER – % OF ALBUMIN IN SUBDURAL POOL TURNED OVER IN 24 HOURS

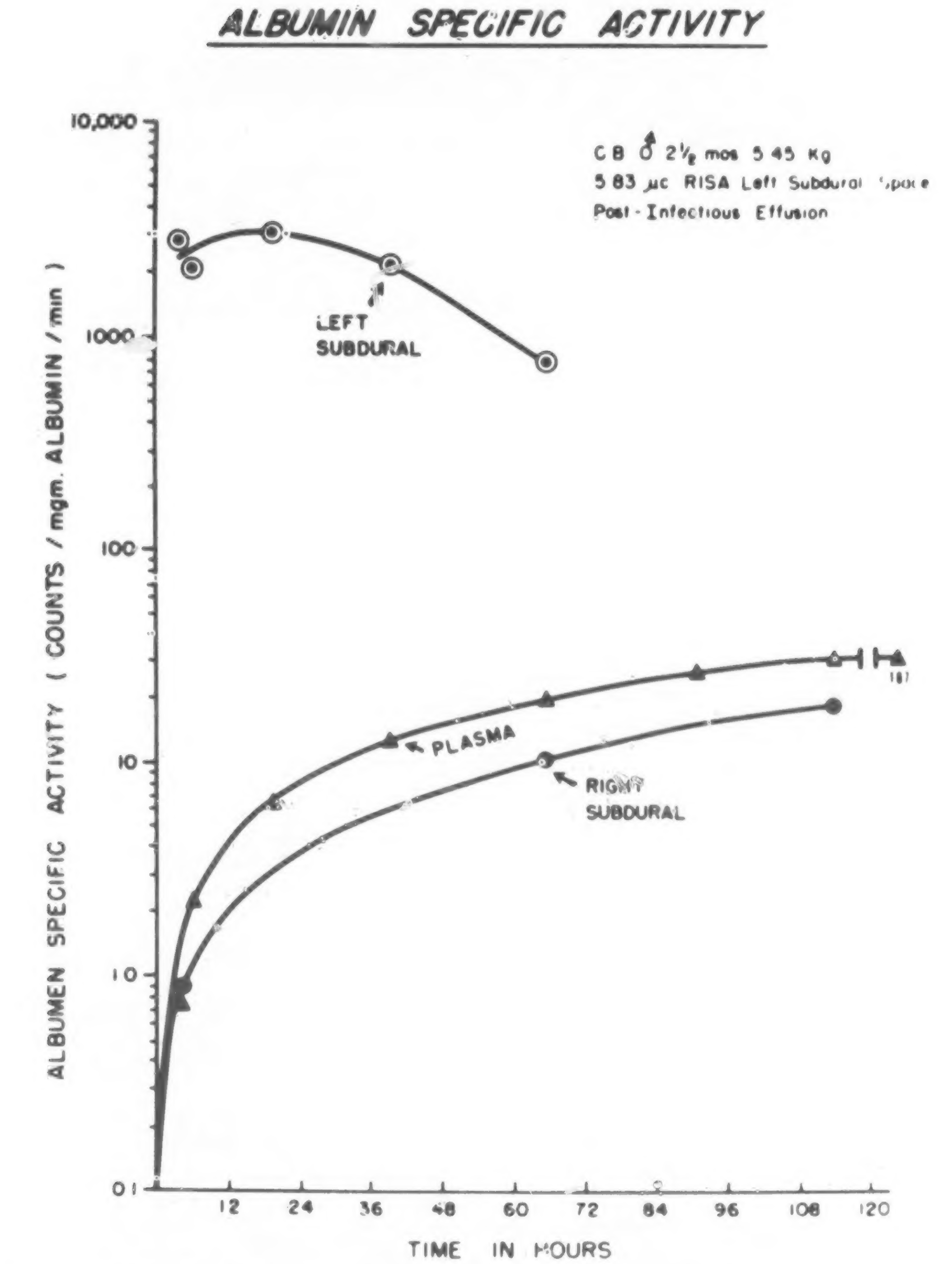


FIGURE 2—Albumin-specific activity in various fluids following left subdural injection of 5.83 μc I ^{131} RISA into infant with bilateral subdural effusions

amount of albumin equivalent to that in the subdural space, the milligrams of albumin turned over in 24 hours, and the percent of the total subdural albumin pool turned over in 24 hours. There was a good correlation between the duration of subdural effusion and both the turnover time, and turnover. The shorter-lived effusions had a faster turnover time and turnover. This suggests that the subdural plasma albumin exchange is slower in the chronic effusion than in subacute ones.

Our hypothesis to account for the persistence and eventual disappearance of subdural effusions is that albumin in the effusions is derived from plasma and traverses the wall of the vascular spaces in the subdural membrane; water and electrolytes accompany the albumin into the space, but their source, which is almost surely plasma, has not been proved. Persistent effusions are accompanied by a continual leak of albumin into the subdural space. With the passage of time, the abnormal permeability of the dural vascular spaces to albumin presumably changes, and more albumin eventually leaves the space than comes into it.

Infants with subdural effusions, preceded by any antecedent event and without evidence of increased intracranial pressure, have been followed by periodic subdural taps and skull transillumination. Twenty-three such infants, treated only by infrequent tapping, evidenced spontaneous disappearance of their effusion over a period of 7 to 123 days. The infants were followed for a period of 9 to 36 months. The mean duration of the effusions was 70 days, with a large standard deviation. Sixty-five percent developed normally, and 35 percent had evidence of some neurologic deficit. None of the patients became worse with the persistent effusion, and all improved to some degree gradually.

The crucial problem with subdural fluid detected beyond a predetermined interval of 14 days is whether persistent fluid in infants with open fontanelles and no clinical signs of increased intracranial pressure will be prejudicial to normal development. The outcome of the above 23 patients is no better or worse than that of patients with multiple antecedent events treated more aggressively. In another study, among 13 infants who were tapped until two successive subdural taps were dry, patients with an excellent outcome yielded fluid for an average of 26 days, while patients with a fair to poor outcome yielded fluid for only 14 days.

Benson reported 67 patients with postmeningitic subdural effusions and noted that there was a slightly lower incidence of poor results in those with subdural effusions tapped repeatedly until dry than in those who were not tapped until dry. Although the trend was suggestive, it was not statistically significant. These observations suggest that asymptomatic subdural effusions without craniocerebral disporportion will not prejudice the future development of infants.

The persistence of subdural effusions in a child with a rapidly enlarging head or a head whose circumference is greater than two standard deviations above normal is a problem of current interest. When this situation exists, the possibility of craniocerebral disproportion and a prolonged effusion presents itself. Craniocerebral disproportion implies that the volume of the cranium is significantly greater than the volume of the brain. Such disproportion is believed to perpetuate a large subdural space and its contained effusion. Whether the existence of this state is deleterious to the patient is not clear.

What volume of subdural fluid can subside spontaneously and thus indicate the absence of craniocerebral disproportion has not been known. The study summarized in Table 3 provides a preliminary answer to the problem. In 8 infants with subdural effusions, the volume of the space was measured by the isotope-dilution method using I^{131} RISA. Five infants were treated with infrequent subdural taps only. In these, the subdural volume ranged from 8 cc to 87 cc, and the fluid disappeared 7 to 54 days after the presumed antecedent event. Two infants treated with repeated taps, craniotomy, and outer membranectomy had fluid for

TABLE 3.—*Relation between subdural volume and duration of effusion—8 infants with subdural effusions*

VOLUME MEASURED BY ISOTOPE DILUTION METHOD (I 131 RISA)

Pt.	Age at onset (mos.)	Antecedent Event	Volume of S.D. Space (mls.)	Fluid Spontaneously Subside	Duration of Effusion (Days)	Clinical Outcome *
C.H.	6.0	MENINGITIS	9	YES	10	G
R.G.	8.0	ENCEPHALITIS	72	YES	14	P
C.B.	2.5	MENINGITIS	52	YES	20	G
A.A.	3.0	TRAUMA	50	YES	40	F
S.R.	4.5	MENINGITIS	87	YES	54	F**
R.M.	3.5	TRAUMA	197	YES-25 DAYS POST-OP+	60	P
D.C.	6.5	CONGENITAL ENCEPHALOPATHY	611	YES-55 DAYS POST-OP+	90	P
J.M.	6.5	IDIOPATHIC	340	NO-DESPITE OP.+ SHUNTED	180	F

KEY—*G—Normal. F—Neurological deficit but can function independently. P—Neurological deficit, cannot function independently.
+ OP.—Craniotomy and removal of membranes.
**—Motor development normal, bilateral deafness, secondary to meningitis or chemotherapy.

25 to 55 days postoperativly. Measured volumes in these two patients were 196 cc and 611 cc. In the final case, a large subdural space (350 cc) persisted after craniotomy and membranectomy. A subdural-pleural, then subdural-peritoneal, and finally subdural-jugular shunt were installed. This resulted at last in a normal rate of growth of the skull, but the large circumference persisted. From this it is apparent that subdural fluid volumes of at least 100 ml will subside spontaneously.

The possible effect of the dural membrane on the prognosis of the patients has been frequently discussed. It is difficult to imagine a deleterious effect from the outer membrane, since it is adherent to the calvarium and not to the brain in the usual circumstances. If one accepts the thesis that the abnormal vasculature of the dural membrane is responsible for the subdural effusion, removal of the outer membrane by craniotomy would presumably remove the cause of the effusion. Dural membranes occurring with subdural effusions are often widely distributed over the dural surface, however, so that complete removal of the membranes by surgery is difficult if not impossible. In addition, following membranectomy, there will be left an abnormal, exposed dural surface. In our series of 62 infants with subdural effusions, 18 of 18 patients tapped following surgical removal of membranes yielded persistent subdural fluid. Also, we have seen evidence of reformation of membrane demonstrated on reoperation of one patient.

Whether the inner or outer membrane can, when adhering to the arachnoid, constrict the brain and prevent its normal growth is a serious problem. The occurrence of dural-arachnoidal adhesions implies a break in the cerebral cortex through a pia-arachnoidal cleft. This would imply focal cortical damage of any sort. Since the inner membrane derives from the outer, and with subsidence of subdural effusion the membranes fuse and finally adhere to the calvarium as part of the dura, constriction of the inner membrane is possible only if a wide subdural space filled with fluid persists. The danger of the inner membrane constricting the brain has been alluded to frequently, but only one instance of such an event has been documented. This case, observed by us, occurred in a 9-month old infant suffering from head trauma. The patient was treated with two craniotomies and a subdural jugular shunt. This severely retarded infant died of pneumonia, and postmortem examination revealed a large subdural space approximately 10 cm wide, with the inner membrane constricting both hemispheres. Diffuse adhesive arachnoiditis secondary to old meningitis, cortical scars presumably from brain contusion, and a communication between the third ven-

TABLE 4.—*Summary of post-mortem findings in 10 fatal cases*

Case No.	Treatment*	Antecedent Incident	Post-mortem CNS Abnormality+
1	1	MISCELLANEOUS	ACUTE INTRACEREBRAL HEMORRHAGE: BRAIN SWELLING
2	1	IDIOPATHIC	WERDNIG-HOFFMAN'S DISEASE
3	1	IDIOPATHIC	DIFFUSE BRAIN SWELLING, POST-CONVULSIVE
4	2	POST-TRAUMATIC	DIFFUSE BRAIN SWELLING AND ACUTE INTRACEREBRAL HEMORRHAGE
5	2	IDIOPATHIC	SUBCORTICAL ENCEPHALOPATHY
6	3	IDIOPATHIC	DIFFUSE BRAIN SWELLING POST-OPERATIVELY
7	3	MISCELLANEOUS	CORTICAL PSEUDOLAMINAR GLIOSIS. ? POST-ANOXIC
8	3	POST-TRAUMATIC	CONSTRICTION OF BRAIN BY THICK INNER MEMBRANE. DIFFUSE ADHESIVE ARACHNOIDITIS. ATROPHIC RIGHT MIDDLE TEMPORAL LOBE AND UNCUS. COMMUNICATING HYDROCEPHALUS THROUGH RUPTURED LAMINA TERMINIALIS.
9	3	IDIOPATHIC	ACUTE MASSIVE POST-OPERATIVE SUBDURAL HEMORRHAGE. NO BRAIN ABNORMALITY
10	3	POST-INFECTIOUS	ACUTE THIN SUBDURAL HEMORRHAGE. MULTIPLE FOCAL INTRACEREBRAL HEMORRHAGES. HEMORRHAGES OF BLOOD VESSEL WALLS. MULTIPLE THROMBI OF SMALL AND LARGE VESSELS (THROMBI ALSO IN KIDNEY. ? SCHWARTZMAN PHENOMENON)

*1 = REPEATED SUBDURAL TAPS; 2 = BURR HOLES AND ASPIRATION; 3 = CRANIOTOMY

+ RESULT OF GROSS AND MICROSCOPIC EXAMINATION OF 9 CASES, GROSS EXAMINATION ONLY IN 1 CASE tricle and the large subdural space through a rent in the lamina terminalis were also apparent.

The need to remove membranes is now being widely questioned. A number of neurosurgeons presently recommend a subdural intracavitary shunt for patients who do not respond satisfactorily to repeated taps. (Schulman and Ransohoff; Till; Yashon, et al.) This is done in preference to membranectomy.

In infants dying with subdural collections of fluid, the pathology of the brain is the pathology of the antecedent event as outlined in Table 4. (Rabe, et al, 1968) This situation is in contrast to that in older children and adults. This important observation, together with the data presented above, has served to direct our attention to treating the manifestations of a symptomatic effusion in infants and not to manipulating an asymptomatic effusion or its membrane.

Conclusions

Subdural collections of fluid have a variable prognosis related principally to the antecedent event. Surgical therapy is needed if increased intracranial pressure occurs, or if a large subdural space is discovered. Otherwise, with careful management of the total patient, subdural fluid spontaneously disappears, and the clinical outcome appears to be dependent upon the presence of brain pathology associated with the initial exciting event.

DISCUSSION

Doctor Barlow: The subject of subdural hematoma has become complex again and I expect there are going to be comments from as many neurosurgeons as there are in the audience, and perhaps equally as many points of view. The two papers are now open for discussion and comment.

Doctor Ransohoff: There is one thing in all of this which I think is an example of fuzzy thinking, and that is the idea that the growth of the subdural hematoma is from damaged capillaries. This is not the course of a hematoma elsewhere in the body. Here is a clot which is located on top of the arachnoid which will lead to a permeable membrane, and I submit that most of the water and most of the increase comes from the cerebral spinal fluid.

The membrane is probably much more permeable to albumin than globulin. The albumin will leak back into the cerebral spinal fluid, and if you analyse the spinal fluid in these kids there is an increased albumin.

The other important point is the expansion of the brain. This is the key. Most of these clots are on the order of a centimeter thick. When you look into the membrane you see the brain come up, and I've seen this enough that I'm going to die before anybody in conversation is going to convince me that the brain isn't better off without the membrane.

Doctor Walker: I want to ask why the brain expands at all. Is this due to an increase in the concentration of water within the brain after removal of a certain amount of fluid from the subdural space? Is it due to increased production of myelin around the nerve fibers? Is it due to an increased number of neurons and glial cells in the brain? Or is it due to enlargement of the ventricles? I think that if one knew the answer to this question, perhaps it would be easier to understand why the brain does not expand.

Under the subdural membrane, in older people—and I don't think we have too much evidence of the pathological state of the brain under the membrane in children—one finds that the brain tissue is very edematous. It is markedly swollen, it has increased vascularity, and these things ought to be just the reverse, because it ought to cause a marked swelling and obliteration of the cavity and we sometimes see it in operation in the individuals who have subdural hematomas.

Now, whether this is true in children I don't know, but I wonder if perhaps in children we might not be dealing with an increase in the water content of the brain, as the result of some condition inherent in the brain of a metabolic nature, or possibly due to a depression of the activity of certain enzymes which produce spinal fluid. As the pressure increases, these enzymes decrease and the spinal fluid is decreased. This might tend to decrease the amount of water and perhaps electrolytes within the central nervous system when a subdural mass is expanding.

The second point I want to comment on has to do with the presence of albumin and globulin within the subdural cavity in the hematomas. If one looks at the tissues in the majority of cases in which membranes come to the laboratory, the clot space between the inner and outer membrane is not a centimeter thick. If you examine this histologically you will find that on the inner surface, the surface adjacent to the cavity—there are many small capillaries. It seems to me that this is the source of most of the albumin that is present within the subdural hematoma and that the spinal fluid, which has a much smaller amount of albumin, would be less likely to be a potent source of the material within the subdural cavity. Consequently, I wonder if there aren't studies on the enzymes in this subdural membrane. What type of enzyme activity is necessary to give rise to this transport?

Doctor Dodge: I tried to wait long enough to sound wise, but I believe that if we try to think about why we are all here and what we are talking about, we will realize that the topic is trauma as an etiological agent in mental retardation and how the subdural problem fits into this.

The membrane doesn't occur first. The membrane occurs in response to fluid, and this seems a very simple concept that hardly needs to be said. Now subdural collections in children obviously have various antecedent correlated phenomena. The simplest one to understand is the child who has severe trauma and develops a big clot in the subdural space. This clot must be removed as a life-saving procedure.

In the child with meningitis, let's say, minor degrees of trauma produce this phenomenon. I think that in the number of the patients who have the so-called cranial cerebral disproportions, these children probably have underlying arrested hydrocephalus; therefore, minor degrees of trauma allow fluid to collect outside the brain as well as inside.

I think it has been shown very clearly by a number of people, including Collins who biopsied subdural membranes, that Rabe's position is correct, that when the fluid disappears the membranes adhere together and rapidly absorb. Now we have seen that these are not dead membranes — dead tissue. The membrane is very thin, usually is very, very thin. To suppose that this can constrict the underlying brain in the usual case, when the brain as it is, grows against the dura, the bone, the scalp, atmospheric pressure, the hat and everything else that is on top of the head—you know, does not really hold water. Occasionally—rarely—one will see very thick inner membranes; in such children there will be evidence of generally increased intracranial pressure. I think that no one can argue that the very occasional, very thick inner membrane should be removed, but by and large, these are growing tissues, capable of further growth, and it is hard, really, to constrict the underlying brain.

So if one doesn't worry about the membrane, then why worry about the whole process? I think the thing that has not been brought out today in this discussion is the problem of the recurrent bleeding, and the recurrent diffusion into the subdural cavity.

Therefore, I think it behooves us to try to aid the natural healing process which is absorption of fluid sticking the membranes together and gradual reabsorption and disappearance. How can we best aid it? Certainly repeated subdural taps in infants can—quote—"dry it up" and all this means is that at the site of a needle puncture, the membranes become adherent. So, based on this information, our general policy is to tap children until they dry and then to carry out an encephalogram, which gives a pretty good understanding of the underlying brain and also of whether there is a significant collection of fluid elsewhere which has not dried up. Usually, you find that there is very little evidence of subdural membrane, subdural fluid, elsewhere.

Now, if you find that a subdural collection really will not dry up (and by this, you know, I mean after you have one resident tap it for a long time—starting with a pediatrician who may get tired, and then a neurosurgeon, or a pediatric neurologist who also get tired, and finally the neurosurgeons say, "Well, we'll do it", and they get tired) then you probably have cranial cerebral disproportions, which, to me, almost always means that there has been a pre-existing situation in that brain. So the best you can do there is to try to stabilize the situation.

We have been able to follow about 20 children with subdural pleural shunts for cranial cerebral disproportion, and have found that over a period of about a year, most of these will eventually clear. Most will eventually reabsorb and the underlying brain or venticular system will re-expand. However, some of these have gone on and developed increased pressure from their underlying hydrocephalus and then this had to be treated.

So, I think that it is really the persistence of the abnormally pliable capillaries within the subdural membranes which are the hazard to the child in terms of its potential for producing the minor degrees of mental retardation, superimposed conceivably on the pre-existing situation. This is a very hard thing to measure, but yet I think it is really the crux of the matter—that those who treat subdurals have got to continue to look at it very hard. That is, it is not satisfactory to me to see a scale showing some coming out very well, because one really has to say, how would the retarded ones have been had the subdurals been handled more adequately? Certainly, this seems to me to be the heart of the problem.

Doctor Page: This is really a very difficult subject and our position here about the membrane, the inner membrane constricting the brain or restricting the brain in its rapid expansion period, is, I believe, something that we can see directly on occasion. Now, it is true, very true, that you can not always demonstrate this in the thin, filmy membrane. On the other hand, this figure of 59% good results that I compiled here was really a very conservative figure in that we followed these patients five full years. I think Dr. Dodge mentioned that they had the advantage of relating this to school performance, which we did, and I think this is at least a sound and conservative figure.

Participant: As a final comment—we have dealt almost completely with subdural hematoma in the usual focus. I would like to point out that there are recognizable subdural hematomas in the postmedian fossa that can occur in the neonatal period, generally presenting with sudden death.

However, on occasion it can present, in five patients that we have collected, as a rapidly progressive hydrocephalus, usually with signs of bleeding in the spinal fluid. This is a potentially remediable lesion and therefore of importance.

REFERENCES

Benson, P., Nyhan, W. L., & Shimizu, H.: The prognosis of subdural effusions complicating pyogenic meningitis. *J Pediat* 57: *670–683,* (*Nov*) *1960.*

Cramblett, H. G.: Recognition and treatment of intracranial manifestions of leukemia. *Amer J Dis Child 97: 805–812* (*June*), *1959.*

Gitlin, D.: Pathogenesis of subdural collections of fluid. *Pediatrics 16: 345–351* (*Sept*), *1955.*

Harvey, S. C. & Burr, H. S.: Development of the meninges. *Arch Neurol and Psychiat 15:545–567* (*May*), *1926.*

Herzberger, E., Rotem, Y., & Braham, J.: Remarks on thirty-three cases of subdural effusion in infancy. *Arch Dis Child 31: 44–50* (*Feb*), *1956.*

Leary, T.: Subdural hemorrhages. *JAMA 103: 897–903* (*22 Sept*) *1934.*

Leary, T.: Subdural or intradural hemorrhages? *Arch Path 28: 808–820* (*Dec*) *1939.*

Moyes, P. D,. Thompson, G. B., & Cluff, J. W.: Subdural peritoneal shunts in the treatment of subdural effusions in infants. *J Nenrosurg 23: 584–587* (*Dec*) *1965.*

Rabe, E. F.: Subdural effusions in infants. *Pediat Clin N Amer 14:831–850* (*Nov*) *1967.*

Rabe, E. F., Flynn, R. E., & Dodge, P. R.: A study of subdural effusions in an infant with particular reference to the mechanisms of their persistence. *Neurology 12: 79–92* (*Feb*) *1962.*

Rabe, E. F., Flynn, R. E., and Dodge, P. R.: Subdural collections of fluid in infants and children. A study of 62 patients with special reference to factors influencing prognosis and the efficacy of various forms of therapy. *Neurology 18: 559–570* (*June*) *1968.*

Rabe, E. F., Young, G. F., & Dodge, P. R.: The distribution and fate of subdurally instilled human serum albumin in infants with subdural collections of fluid. *Neurology 14: 1020–1028* (*Nov*) *1964.*

Shulman, K., & Ransohoff, J.: Subdural hematoma in children. The fate of children with retained membranes. *J Neurosurg 18: 175–181* (*Mar*) *1961.*

Till, K.: Subdural hematoma and effusion in infancy. *Brit Med J 2: 400–402,* (*Aug*) *1968.*

Yashon, D., et al.: Traumatic subdural hematoma of infancy. Long-term follow-up of 92 patients. *Arch Neurol 18: 370–377* (*Apr*) *1968.*

THE BATTERED CHILD

James S. Apthorp, M.D.
Childrens Hospital of Los Angeles
Department of Pediatrics
University of Southern California School of Medicine
Los Angeles, California

This paper briefly reviews 263 cases of inflicted trauma diagnosed at the Childrens Hospital of Los Angeles during the past eight years. The diagnosis was made on the basis of the medical findings in conjunction with the history, age and development of the child. Attention is focused on head trauma in this series, without reporting the additional injuries to soft tissue and skeletal structures in many of these cases. All were reported to the police in accordance with California State law.

Table 1.—*Inflicted trauma*

LOS ANGELES CHILDRENS HOSPITAL

Total Cases	263
Total Head Trauma	138
Major Head Trauma	79
Minor Head Trauma	59
Male	70
Female	68

Table 1 demonstrates the incidence of head trauma in this series; there is no sex preference among these children.

Table 2.—*Major head trauma*

AGE	0-3 mo.	3-12 mo.	12-18 mo.	18-24 mo.	2-5 yr.	>5 yr.
Bilateral Subdural Hematoma	14	7	1	1	2	
Unilateral Subdural Hematoma	3	7	1	1		
Cerebral Contusion	4	5	1		3	1
Skull Fracture	7	12	4		2	1
Subarachnoid Hemorrhage		1				

The age incidence of major head trauma shown in Table 2 contrasts with the age incidence of minor head trauma shown in Table 3.

TABLE 3.—*Minor external head trauma*

AGE	0-3 mo.	3-12 mo.	12-18 mo.	18-24 mo.	2-5 yr.	>5 yr.
TOTAL	9	14	13	4	11	8
Bruises						
Lacerations						
Abrasions						
Burns						
Subgaleal hematoma						
Associated with major head trauma (concurrent)	7	15	6	2	5	1

Table 4 indicates that inflicted trauma with serious head injury does result in death, or permanent neurological or mental handicap, as might be expected.

TABLE 4.—*Residual handicaps of those known to follow-up*

Death		13
Severe M. R. (placement)		5
Moderate M. R. (E.M.R.)		2
Developmental delay (improving)		7
Spastic quadriplegia		5
Spastic C-P		3
Hemiparesis		3
Optic atrophy		3
Blindness	Total	2
	Partial	5
Hearing Loss		1
Behavior Disorders		4
Seizures		5

Not all of these children have had follow-up evaluations, but the majority of those having serious head trauma were seen for medical or neurosurgical examination after discharge. Psychological testing has been accomplished in a very small number. Therefore, we do not have adequate measures of behavioral function in the majority of the children who have been victims of inflicted trauma.

Although the incidence is small in this series of recognized cases, inflicted trauma represents a significant segment of physical injury causing mental retardation.

DISCUSSION

DOCTOR DODGE: I have ben interested in this problem for some time not only as a physician but as a former Director of the Massachusetts Society for the Prevention of Cruelty to Children. One of the points which I think bears emphasis repeatedly is that, in the Boston series at least, half of the affected children had been at a medical facility for the treatment of trauma before and had returned to the home. I think this a point which needs stressing, particularly when we're confronted with major efforts on the part of social workers and others to maintain the integrity of the family group.

The second point is one brought out today—the lack of correlation between evidence of external trauma and internal trauma. In part, this may be due to the fact that the relatively minor bruise has cleared. Another hypothesis is that some of these young infants, who frequently are annoying to parents because of their fretfulness and crying, are in fact shaken very vigorously rather than being directly bumped against a solid object. Under these circumstances I would submit the possibility that there might be shearing of vessels traversing subdural space.

Doctor Barlow: Every State has a law, yet the reporting by law does not suffice. The law is not the point. It is the follow-up, as Dr. Dodge so properly pointed out—really picking these cases up and doing something about them when they occur because another chance may never come. The fatality rate is, I think, even higher in many series than in this one of 10 percent. I think that it is terribly important to realize that this is a repetitive phenomenon. Somehow one has to treat the entire family, because otherwise this is really an extremely critical, serious, often fatal problem.

Participant: I wonder if some of the incidence of mental subnormality and neurological handicap might in a sense instigate the abuse. So, I would wonder about the statistics.

Doctor Barlow: In our series of 100 cases it was very obvious that about 15 percent of these kids were retarded or had cerebral palsy before the injury and that this may be provocative to the parent.

AN INTERDISCIPLINARY PROSPECTIVE STUDY OF HEAD TRAUMA IN CHILDREN

PERRY BLACK, M.D., DIETRICH BLUMER, M.D.,
ALFRED WELLNER, PH.D.,
J. J. JEFFRIES, M.B., B.CH., AND A. EARL WALKER, M.D.
Neurological Surgery
Johns Hopkins University School of Medicine and Hospital
Baltimore, Maryland

Currently in progress, this longitudinal clinical study seeks to investigate the early and long-term effects of head injury in children from birth through 14 years. The project incorporates four relevant areas—neurologic, EEG, psychiatric, and psychometric—to determine the natural history of head injury within each and to evaluate their interrelationships. Particular attention is being directed to the age-effect relationship—the effect of the age of the individual at the time of head injury in relation to the ultimate neurologic behavioral, and intellectual outcome. Such factors as coma, skull fracture, or abnormal EEG, which may conceivably have prognostic value in terms of the functional end-result will be considered. The concept of "severity of injury" would then become a function of the *prognostic* factors, as determined by retrospective analysis.

Children are registered in the long-term project when they are admitted to the hospital for treatment of their acute injury. The minimal criterion for entry in the study is a history of trauma associated with at least one of the following, which serve as bona fide evidence of head injury: loss of consciousness (of any duration); skull fracture (radiographically or clinically evident); neurologic deficit or seizure.

Apart from medical and surgical care, the evaluation of each child includes a study of psychological, psychiatric, EEG, and neurologic factors. After discharge from the hospital, the child is followed on an outpatient basis, with a visit at three months and subsequently at five yearly intervals. The data are coded for computer analysis.

Siblings of the head-injured children serve as controls. They represent a matched sample for genetic and socioeconomic factors. As a group, the siblings are matched in accordance with the age-sex and racial distribution of the probands.

Preliminary results. The present report is based on a preliminary analysis of some characteristics of the first 107 children studied for up to two years. The bulk of cases (70.9 percent) ranged between 2 and 10 years of age. The sex ratio was approximately 3:1 males to females. Almost 60 percent of the injuries were related to falls, about 30 percent to motor vehicle accidents, and the remainder to objects striking the head. Duration of coma in 88.6 percent was 0 to one hour.

Some 34 percent of the patients presented with such neurologic dysfunction as motor or cranial nerve involvement. An additional 36 percent exhibited only coma. By the time of discharge from hospital, all coma cases had recovered consciousness. Other neurologic deficits persisted in 24 percent; these declined further to 15 percent within three months and remained fairly stable thereafter (within the 2 year period of observation). A large majority of the residual abnormalities were minor, such as unilateral hyperreflexia.

Correlation of specific early posttraumatic manifestations with neuropsychological sequelae. About 52 percent of patients who presented with a neurologic deficit exhibited hyperkinetic behavior one year later. This represents a statistically significant difference from the neurologically normal children, of whom only 25 percent were later hyperkinetic.

As in the case of neurologic status, an abnormal EEG (slowing, disorganization, paroxysmal activity) on the initial examination was predictive of a higher incidence of behavioral dysfunction than a normal tracing. The behavioral traits included hyperkinesis, irritability, and poor attention span.

An increased frequency of posttraumatic hyperkinesis was found in children with a history of normal pre-injury kinesis. None of the children who sustained long coma (1 hour to 1 month) later developed hyperkinesis. No statistically significant correlation could be found, however, between the initial level of consciousness and subsequent hyperkinesis. Approximately 20 percent of the head-injured sample had a history of preinjury hyperkinesis. A steady decline in the frequency of this trait was observed during the posttraumatic period. This unexpected finding was independent of the initial level of consciousness.

Comparison of I.Q. for initially conscious and unconscious children failed to reveal a statistically significant difference. The Wechsler Intelligence Scale for Children (WISC) was employed for this analysis and was limited to the gross Full Scale, Verbal, and Performance scores. It is conceivable that further analysis, employing the WISC subtests, may show significant differences. In addition, future comparison with the control subjects will indicate whether the postraumatic I.Q. scores of the probands differ from the non-head-injured population.

DISCUSSION

Doctor Carlson: I'm particularly interested in your analysis of hyperkinesis. We have discussed hyperkinetic behavior several times during the course of the conference but I find it difficult in my own clinical experience to measure this objectively. I wondered what criteria you were using to project these measurements?

Doctor Black: This is an excellent point. I am glad you raised it, though it may prove embarrassing. This question clouds the whole psychiatric issue. Our psychiatric inventories, our psychiatric examinations, are the most subjective of all the examinations that we have—the neurological, the EEG, the psychometric. I think we have a good deal of confidence in these measurements, but it is in the psychiatric realm that we are, perhaps, on shaky ground.

We depend largely upon the judgment and the objectivity of our psychiatrists who examine all of these children. We have two psychiatrists, and we hope that they have established in their own minds some specific criteria for what they will regard as hyperactive. In general, I might say, that the children who are reported here as being hyperactive—looking at them even as a neurosurgeon—these kids are *really* hyperactive. They pose problems during the neurological examination. They are the children whose parents spontaneously report, "I just can't keep this kid still." We have reports from the teachers, and the principals and the school board, who are sending us letters about these children; "Please send us some advice on how to manage these children".

Doctor Meyer: This is a very exciting study and I think that Dr. Black and his colleagues are to be congratulated on it. It is very evident that this is a high-risk population you have here. Perhaps a more perfect control would be age, sex, social class, matched in the neighborhood but not in the family. I say this because I think that epidemiologically you're a little bit biased by the high rate of pedestrian injuries in the lower socio-economic group.

Observer error of hyperactivity may be subject to 100 percent error in the best of hands, particularly in a study where the psychiatrist evaluates the child. Adding to the problem is the fact that in this group of children there are those who are hyperkinetic to begin with; that's why they got into the accidents. Too, it is difficult to get a reliable history from parents who feel a little guilty about the injury, particularly, with an interviewer like a psychiatrist.

Participant: Does your study allow you to comment on the question of whether or not any of these children became mentally retarded in some sense?

Doctor Black: Well, I only have some subjective impressions at this point. There are a small number of children who end up in institutions but these are mostly the suspect group of battered children. A small proportion do end up with what I suppose you might call mental retardation, on the basis that they require special schooling.

Participant: You showed us some data regarding coma. I wonder if you would be good enough to give us your criteria for coma, particularly for the end point when the coma is no longer there. Secondly, you said you were determining both the coma and posttraumatic amnesia. It would be helpful if we had your criteria for post-traumatic amnesia, and it would be very useful were you to correlate coma with post-traumatic amnesia, to see what the relationship is. To my knowledge no one has ever done this.

Doctor Black: In the first place, regarding our criteria for coma, this again is a very difficult issue. We have tried to make as efficient criteria as we possibly could. I, personally, evaluate this particular aspect in the cases of children who are momentarily unconscious. I take all of this history myself from parents and from children who can speak and have some understanding, and I get some idea from them as to how long they may have been in coma.

Then I pull all of the information together and come up with some figures. quantitatively, on coma, and these are the criteria. These children do not have any psychological response to the environment. They may be thrashing around, but there is no deliberate movement. There may be sounds, but no words. In case of young infants who may have fallen off dressing tables and so on, the measurement is taken from the moment of the blow until the time that the child has uttered a cry.

Now, with respect to post-traumatic amnesia, we initially did a pilot survey of the problem and found that we could not employ the same criteria suggested by Symonds and Russell because of the difficulty in communication. Instead we try to determine the duration of what we call confusion; this is defined as that period independent of the coma when the child's reaction is found inappropriate for the situation.

Obviously what is appropriate for one child may not be appropriate for another. You get into problems of children with defective or immature speech where we cannot ask simple questions such as, "What is your name?" Additionally, we're trying to get at the three spheres of orientation—place, name, date—which mean that we have to rely on the child's knowledge and general appropriateness of response. If the child is simply crying, we do not regard this as confusion because we feel that this might be quite appropriate for the child in a strange place—in a hospital room or in an accident ward.

In the older chlldren with whom we and the parents can communicate, it becomes much simpler. It becomes a matter of identifying with the parent—at what point the child first recognized the parent, the point at which the child indicated that he was aware of what was going on. Here we come closer to what Symonds and Russell have established as post-traumatic amnesia.

18280

INTELLECTUAL SEQUELAE IN CHILDREN AND ADOLESCENTS FOLLOWING PROLONGED COMA DUE TO ACCELERATION CONCUSSION

FREDERICK RICHARDSON M.D., M.R.C.P.
Department of Pediatrics
Johns Hopkins University School of Medicine
John F. Kennedy Institute for the Habilitation of the Handicapped Child
Baltimore, Maryland

Disability following head trauma and the objective evaluation of residual intellectual defect and subjective complaints of patients pose an increasing problem. Although penetrating injuries of the brain cause many sequelae, the most formidable and yet often ill-defined problems follow closed head injury accompanied by loss of consciousness.

Transient loss of consciousness due to concussion is followed by neuronal loss and structural damage, and the duration of loss of consciousness could be a measure of the degree of cerebral injury, Symonds suggested. Russell and Smith refined Symonds' concept: The duration of post-traumatic amnesia in a patient with nonfocal closed head injury is directly related to the degree of structural alteration and therefore to the ultimate prognosis.

Among the serious stresses on the brain in acceleration concussion are the brain's own inertia under conditions of excessive acceleration or deceleration and large strains with shearing near the junction between the white and gray matter resulting from their different densities. Photographs of the brain at impact (Pudenz and Shelden) showed conclusively the centrifugal rotation of the brain and cerebral mass movement.

Microscopic studies by Strich demonstrated that nerve fibers are torn or stretched at the time of accident by the rotational forces. She also found evidence that many fibers are stretched rather than torn, suggesting that reconstitution or reacquisition of previous function may be possible to some degree.

The symptoms that continue after the conclusion of post-traumatic amnesia are mainly subjective: anxiety, irritability, difficulty with sustained mental concentration, impaired memory, and excessive liability to fatigue. These may, however, have a physical basis (Symonds).

In the children and adolescents I have followed, the above symptoms were constant. Severity was related directly to the period of post-traumatic amnesia. Coma was protracted (median 28 days), and post-traumatic amnesia persisted for several weeks (median 49 days). All patients developed severe academic difficulty due to distractability, poor comprehension, and concrete and perseverative performance. The majority had become borderline defective in intelligence, showing a wide scatter in scores on different test items. In all patients new personalities emerged, often with characteristics less pleasing to the parents.

Recently I have encountered more severely retarded acceleration-concussion patients whose physical symptoms from the trauma had to be treated with such resuscitative means as closed cardiac massage or mouth-to-mouth respiration. The more severe retardation (IQ 30-60) and potential increase in young vegetative survivors may be due to the combined insults of concussion and hypoxia.

Even when measured IQs are average or near average following prolonged post-traumatic amnesia, personality and emotional factors may be much more significant in the patient's return to a productive life. There is also an age-dependent phenomenon relating directly to the speed and degree of recovery. Infants or children up to 4 years old with a single exposure to acceleration-concussion seem either to recover rapidly and completely or to die of cerebral edema. Prolonged vegetative survival in this age group is rare. Children between 5 and 12 years make the best recovery, even following prolonged coma or post-traumatic amnesia. Vegetative survival following uncomplicated acceleration concussion in this group is also uncommon. Slower recovery with personality disorders or post-traumatic psychotic syndromes may occur in postpubertal patients.

How common and severe mental incapacity is, is still an open question. In Great Britain, Lewin estimated that about 1,200 of 7,500 patients with post-traumatic amnesia of more than 24 hours work at a simple level or require special care. Lancet has reported a quarter of a million head injuries a year; and London has estimated that about half of 1,000 persons newly disabled every year will never work again.

Many such patients fall into the category of the mentally retarded as defined by the President's Task Force on Education and Rehabilitation. Considerably more study is needed if prevention, rehabilitation, and care is to be provided.

DISCUSSION

DOCTOR DODGE: Though some of the figures that I give may not be precise I thought it appropriate to comment on a recent paper by Carlsson and associates, a Scandinavian report (J Neurosurg 29–242–251, 1968), which related to this whole question of mental restitution following serious head injuries at various ages. In this particular study, which was carried out retrospectively for from 1 to 10 years, these authors attempted to relate mental restitution on a percentile scale on the vertical axis, in days of coma.

These authors defined mental restitution as the return to a functioning state of the individual in work and in society. This is not defined in great detail and obviously did not give attention to some of the very critical and very important functions which should be assessed and which have been alluded to by Dr. Richardson. One point was that there was a distinct difference among the groups, depending upon the age of the individual, so that if one had looked at the group from 50 plus years, and the group from 30 to 50 years, one saw that the longer the duration of coma, the less likely was full restitution of mental function in the older age group.

The writers evolved a regression line for the correlation of duration of coma in hours and the age in years with the restitution time. Restitution was close to

100 percent in the group zero to 10 years. The severity of the coma or the duration of the coma was considerably less on the average than in the cases shown previously by Dr. Richardson and commented upon today; half had regained consciousness by 32 hours, so that clearly the severity of the injury was less.

The problem is, it seems to me, that any study which purports to relate to the ultimate disability, must take into account these very important points stressed by Dr. Richardson. School performance obviously requires concentration, lack of distractability, and the maintenance of a personality which is consistent with adaptation to the school and learning situation. I would think that his comments underscore the necessity for very careful studies relating to functions in these areas, and I think it's here that what's called psychology cannot be divorced from what might be called neurology, and I feel that these really are in many ways one and the same.

The additional evidence Dr. Richardson has gained on the seriousness of cardiorespiratory failure, I think, also underscores the fact that a multitude of abnormalities are at play in the production of the very serious types of brain injury which result in institutionalization and which may result in some of the pathologic changes demonstrated this morning.

But clearly we're interested not only in these, but in many ways, even more interested in what I suspect is the bulk problem, namely, disorders in which the functioning which ultimately may permit the individual to remain in society but may in the long run be the problem which causes a major disability in the epidemiological sense.

Doctor Adams: In the adult head injury group, we have discerned two principal types of syndrome. In one that we call post-traumatic nervous instability, we include anxiety, and of course the depressive mood, the inability to settle down, to settle down and work.

Another has been a syndrome with variable neurological deficit. As far as I know, the syndrome that is common with neurological deficit has in nearly all instances been a very severe injury and there is quite a close correlation between severity of injury and this residue. As far as the post-traumatic nervous irritability syndrome is concerned, there has been almost no correlation between the severity of the injury and its curves.

In fact, it's been very evident in individuals who were never comatose, and has been completely absent in individuals who have been in coma for a long period. There has been much discussion about what this post-traumatic nervous instability means, whether it's psychologically determined or not. In a way, you have a chance in this childhood material to look more carefully.

My question is, what is the age range in this syndrome—post-traumatic nervous instability? We were told, and I've been responsible for saying, that it's very rare in children until they begin to approach puberty, and increases in frequency during adolescence. Is that true? I would feel that there was some advantage to keeping this syndrome somewhat apart from all of the others, not to lump together true intellectual deficit with this syndrome. One reason is that they have not gone together; the other is that most of the cases of this post-traumatic nervous instability recovered, and are believed to function quite normally later. Is that true of children too?

Doctor Jacobson: I'd like to express my feelings regarding this matter because I have been following a group of patients for 10 years. This will be reported in detail at the forthcoming conference on, "Later Effects of Head Injuries". As far as the epidemiology goes, these patients are from metropolitan New York City where you have minor head injuries with coma of less than one hour in the vast majority.

Now when you examine and take a history from these children, patients, and their families, you find that it is very difficult to find the duration of coma or the duration of the post-traumatic amnesia. Frequently it's not present in the minor head injuries and there will be effects afterwards, so I have been impressed that when you start dealing with minor head injuries, the duration of the lapse of consciousness is a highly variable thing, even when there is one examiner. Now as in this group, particularly in the children, the difficulty in memory and inability to do school work was uncommon, even when the period of loss of consciousness approached one hour; if there was a period when they had loss of memory, this passed away very rapidly.

Symptoms, possibly psychological in origin such as anxiety, personality difficulties, insomnia, nightmares, were equally present in all of the groups of loss of consciousness, with a decrease in the group in which there was a longer period of loss of consciousness. This anxiety and related symptoms remained about the same in all decades.

However, memory defect increased with age, and also increased with the duration of the defect in consciousness, so I think there is evidence here to indicate that we're dealing with two different groups.

Doctor Russell: Sir, I would like to support strongly the suggestion that we need to plan prospective socio-medical studies in communities. It seems to me that it's very easy and very tempting to become mesmerized by the medical as opposed to the sociological aspects of this whole problem we're discussing.

Perhaps this is because the medical aspects in certain areas seem to be more precise, as opposed to the sociological side. I think we know far too little, for example, about the medical penalities of being born into the lower socio-economic groups, and this interests me greatly. Recently, in England, I've been trying to find out about some of the penalities attached to being born into the lower socio-economic groups. The information largely isn't there. In Newcastle we do have a certain amount of information from a 1,000-family survey. We know for example, that the episodes of infection, so far as a child is concerned, are greater as the parity of the family goes up, as the socio-economic scale goes down. And I would guess that accidents to a child either at home or outside will be more frequent as you come down the socio-economic scale. I don't think that we know enough about this.

Again, I would suggest that after a bang on the head or whatever it is, if you happen to be brought up in a very overcrowded home, where there are three or four people living in a room, where father is coming home drunk every other night, then you're more liable to get instability and troubles, and so forth, and I would press for a very detailed sociological approach to this problem. This, I think, would be most helpful, and I hope that participants in this meeting, throughout all of their deliberations, will keep in mind the sociological aspects of these problems. I should add that we are much aware of the clustering of all of these factors, but to attempt to dissect them and bring them out requires more wit than we seem to have.

REFERENCES

Alquié: Etude clinique et expérimentale de la commotion tramatique ou ébranlement de l'encéphale. *Gaz Méd Paris 20, 1865.*

Denny-Brown, D.: Sequelae of war head injuries. *New Eng J Med 227: 771,* (*Nov 19*) *1942.*

Denny-Brown, D., and Russell, W. R.: Experimental cerebral concussion. *Brain 64: 93–164* (*Sept*) *1941.*

Ferrari, A.: Sulla commozione cerebrale: observazione ed experiminti. *Spallanzani 11: 169–196, 1882.*

Holburn, A. H. S.: Mechanics of head injuries. *Lancet, 2: 438–441* (*Oct 9*) *1943.*

Holburn ,A. H S.: Mechanics of brain injuries. *Brit Med Bull 3: 147–149, 1945.*

Severe head injuries. *Lancet 1: 514, 1968.*

Lewin, W.: Rehabilitation after head injury. *Brit Med J 1: 465–470* (*Feb. 24*) *1968.*

London, P. S.: Some observations on the course of events after severe injury of the head. *Ann Roy Coll Surg Eng. 41: 460–479,* (*Dec*) *1967.*

President's Panel on Mental Retardation: *Report of the Task Force on Behavioral and Social Research.* U.S. Dept. Health, Education, and Welfare, March, 1964.

President's Panel on Mental Retardation: *Report of the Task Force on Education and Rehabilitation.* U.S. Dept. Health, Education, and Welfare, August, 1962.

Pudenz, R. H., and Shelden, C. H.: The lucite calvarium—a method for direct observation of the brain. II Cranial trauma and brain movement. *J Neurosurg 3: 487–505* (*Nov*) *1946.*

Richardson, F.: A follow-up study of children and adolescents after protracted coma. Some effects of severe head injury. *Develop Med Child Neurol 5: 471–482* (*Oct*) *1963.*

Russell, W. R., and Smith, A.: Post-traumatic amnesia in closed head injury. *Arch Neurol 5: 4–17* (*Jul*) *1961.*

Smith, A.: Duration of impaired consciousness as an index of severity in closed head injuries; *Dis Nerv Syst 22: 69–74* (*Feb*) *1961.*

Strich, S. J.: Diffuse degeneration of cerebral white matter in severe dementia following head injury. *J Neurol Neurosurg Psychiat 19: 163–185* (*Aug*) *1956.*

Strich, S. J.: Shearing of nerve fibres as a cause of brain damage due to head injury. A pathological study of twenty cases. *Lancet, 2: 443–448* (*Aug 26*) *1961.*

Symonds, C. P.: Observations on the differential diagnosis and treatment of cerebral states consequent upon head injuries. *Brit Med J 2, 829–832,* (*Nov 10*) *1928.*

Symonds, C. P.: Concussion and its sequelae. *Lancet, 1: 1–5* (*Jan 6*) *1962.*

SUMMARY AND FUTURE PLANS

Philip R. Dodge, M.D.
Department of Pediatrics
Washington University School of Medicine
St. Louis, Missouri

It's perfectly obvious to all of us who have had the pleasure of being here during the past 15 hours, not to mention the many hours spent in fruitful discussions at breakfast and lunch and over martinis, that the amount of material covered can scarcely be summarized briefly. I shall try, however, to separate the summary into two parts: (1) *postnatal injury,* and (2) the problems of *perinatal trauma.*

The magnitude of the medical and social problem of head injury in children requires very little emphasis. Dr. Caveness made it abundantly clear that large numbers of children suffer head injuries in the course of daily activities. In a relatively short period of time almost 3 million children, three-quarters of whom were under the age of 6 years, were injured. This represents approximately 3 percent of the population at risk in this particular age group.

It seems clear from the discussions at this conference that there is an undeniable relationship between postnatal trauma and mental retardation, and that severely injured individuals who survive may be left with irreparable brain damage; as a consequence, they cannot function well, learn, and adapt to society. They are, by definition, mentally retarded. This applies primarily to the very seriously injured patients with significant neurologic deficits in addition to learning problems.

Dr. Black reviewed what may be the first study of children in which not only were factors surrounding an injury investigated, but also intimate details of the immediate post-injury period and a controlled follow-up study. The importance of paying attention to the individual patient and to the course of his recovery from trauma should not be overlooked. Data from a single case may be lost in a statistical analysis because of the total size of the sample, but be of biological significance.

The question of definition as it applies to problems of altered consciousness in children was alluded to by Dr. Black. In many situations one has to use terms of describing behavior rather than some of the familiar standard nomenclature. In the young child, you need to know with certainty that you are dealing with altered consciousness directly due to the concussive force and not just profound sleep commonly encountered in severely stressed and over-tired children.

There are other problems surrounding acute head injury that demand further study and elucidation—the problem of flash edema, for example. What are the factors in the immature human brain that permit massive swelling to occur in a relatively short period of time and that too frequently lead to death? In relation to this, Dr. Richardson stressed that, due to improved methods of resuscitation and better equipment, an increasing number of patients severely damaged by trauma per se are enabled to survive. As he put it, "This is not an unmixed blessing." It is one that has to be investigated in future studies.

It is imperative that our society assume responsibility for the study and prevention of injury to the heads of children. To do this will require large amounts of money, personnel, and programming. In his epidemiologic report, Dr. Caveness set forth some tentative proposals, enumerating the factors essential for the achievement of this particular goal.

The perinatal trauma problem is a much more complicated one. Injury secondary to a direct blow we can all understand. But early in the discussion, the definition of perinatal trauma was the source of disagreement. In the final analysis, perinatal trauma appears to refer to all events occurring during the perinatal process that could adversely affect the function of the nervous system acutely, and that could, at a later period of time, include mental retardation as one of the important sequelae.

The major problem at this point in time, as far as damage to the nervous system with permanent sequelae is concerned, would appear to be perinatal trauma rather than head injury sustained in the postnatal period. Perinatal events rather than postnatal trauma were conceded to produce more often mental retardation, cerebral palsy, epilepsy, and other forms of neurologic dysfunction.

Reports from Dr. Clifford showed that a fairly significant percentage of the population under study in the collaborative project in Boston had some difficulties at a later period of life. This represented less than 1 percent of all infants in the group. If one analyzes those data, one sees that about half of the individuals involved had anoxia as a primary problem; the other half, direct mechanical trauma. The difficulties of separating these two are evident.

The estimates by the Boston pediatricians who observed these infants in the neonatal period were that a larger percentage, possibly 4 percent, were likely to develop neurologic difficulties later. In other words, observations in the perinatal period lacked a certain predictive quality. Dr. Desmond also spoke of this problem.

The question of underlying pathoanatomic changes in trauma during the perinatal period evoked much discussion. Not that there is major disagreement among the various disciplines as to the types of lesions found or the causes of death in children who die immediately or some time after a presumed or known abnormal event at delivery—the real question concerns their pathogenesis. What are the causes of these well-described, well-recognized pathologic findings?

It was noted in the chronic material that there were at least three major types of pathologic change, with considerable overlap among these. There are some cases in which a generalized or laminar necrosis of cells in the cerebral cortex is found; the hippocampal region is especially vulnerable. There are other cases with status marmoratus—marbling of the diencephalic structures, the thalamus and, to some extent, the cortex. There are still others, probably the largest group, in which necrosis and, at a later stage, gliosis of the cerebral white matter, especially in the periventricular regions, are prominent.

In the acute stage, a variety of changes were described and a variety of words used in discussing these changes. Laminar cortical necrosis was stated to occur early in life if sufficient time elapsed after the insult for the development of this cortical change. Damage to upper spinal cord and brain stem was stressed by Dr. Yates and commented upon also by Dr. Towbin.

As to the pathogenesis of these changes, the recurring themes of hypoxemia, associated acidosis, stasis within vessels or thrombosis of veins and arteries, infarction, and infarct necrosis were heard. In relation to this, Dr. Towbin stated that anoxia is the primary problem and that in most instances this is consequent upon placental dysfunction of one sort or another. This leads to stasis and at times to thrombosis in vessels. He also maintained that the internal venous system of the premature child is most susceptible; in the full-term infant the superficial aspects of the hemispheres are more vulnerable. Dr. Malamud took issue with this, pointing out that in his experience, at least 70 percent of patients—if I remember the figure correctly—demonstrating periventricular leukomalacia and other white-matter lesions were from the full-term populations. Clearly this was a point of disagreement.

Dr. Adams and others stressed the interaction of ischemia and anoxemia. He believes that neither alone can explain the distribution and nature of these observed changes.

Subarachnoid hemorrhage occurs in 10 to 20 percent of newborn infants. Clinical data were presented by Dr. Carlson and this was supported by the postmortem observations of Dr. Adams. The presence of subdural hemorrhage is an acknowledged finding in this age group. It was described as "blood in relation to tentorial and other major venous sinuses, and also as blood in relation to the internal cerebral venous system."

Dr. Oski discussed the possible influence of factors modifying clotting in the premature baby. He indicated that the premature baby does, in fact, have some deficiencies in clotting mechanisms, but the data assembled to date fail to suggest that this plays a major role in the development of the intracranial bleeding episodes particularly common in this premature age group.

It was clear from the studies of Dr. Sumi that tissue characteristics of the immature nervous system favor dissolution and cavity formation in response to injury. In older animals and in adult man dense glial reaction is characteristic and cavity formation uncommon. He pointed out further that the timetable of elaboration of cellular elements and removal of tissue in response to injury in the newborn rat is much more rapid than is seen in adult animals. The high water content of the infant brain as an important factor in its rapid dissolution was stressed repeatedly. The paucity of dendritic and astrocytic processes in immature brain was also mentioned. Anyone who has held an infant brain in his hand can readily attest to the jello-like consistency and friability of the organ.

The studies of Dr. Hicks pointed to the capacity of the young animal to compensate functionally for large, surgically induced losses in brain mass. I would hasten to point out, however, that this is not always predictable; in comparison with the adult, the response is variable. Also, very specific tests to bring out these deficiencies are of the utmost importance. In the long-term evaluation of infants who have suffered from either perinatal or later-life trauma, methods to evaluate brain function, beyond those employed in the more standard psychological tests, should be exploited.

Obstetric factors are clearly at the heart of the entire perinatal problem. Drs. Churchill, Willerman, and Rosenbaum reviewed data correlating the mode of delivery with subsequent I.Q. measurements. Although in these studies there is no question that there are differences in mean intelligence quotients among groups of infants delivered in different ways, the reasons are not at all apparent. There is a statistically valid association, but there still remains the haunting question of the biological significance of these findings. It was evident to me, and I suspect to most of you, that the crucial data permitting us to relate the events transpiring in the perinatal period to brain damage and subsequent disability were lacking in the majority of studies, even though they were part of a prospective study.

The very sophisticated methods of Drs. Hon and Caldeyro-Barcia did demonstrate, I think, the possible applicability of such methods to the study of the all important physiologic and biochemical processes of pregnancy, labor and delivery. I would submit that the future lies in developing units or centers throughout this country that are capable of dealing with the complexities inherent in such sophisticated programs.

Such perinatal centers should bring together obstetricans, pediatricians, biochemists, biophysicists, and other medical specialists who will focus their efforts upon this most vulnerable period in the development of man.

EDITED MEDLARS BIBLIOGRAPHY 1965–1968
PHYSICAL TRAUMA AND MENTAL RETARDATION
CLINICAL STUDIES

1. Abdank, R.: Covering of dural defects in open cerebrocranial injuries by means of preserved dura. (Ger.) *Zbl Chir 91:21-22, (Jan) 1966*
2. Abdank, R.: Covering of dura defects in skull-brain injuries with preserved dura. (Ger.) *Zbl Chir 93:1367-1369, (28 Sept) 1968*
3. Abercrombie, M. L., Lindon, R. L., and Tyson, M. C.: Direction of drawing movements. *Development Med Child Neurol 10:93-97, (Feb.) 1968*
4. Abrams, A. L.: Delayed and irregular maturation versus minimal brain injury recommendations for a change in current nomenclature. *Clin Pediat (Phila) 7:344-349, (June) 1968*
5. Achslogh, J.: Emergency therapeutic procedure in cranial injuries in children. (Fre.). *Scalpel (Brux) 118:381-394, (8 May) 1965*
6. Adams, A. E.: Some diagnostic and therapeutic problems of acute craniocerebral traumas (Ger). *Deutsch Med Wschr 92:1173-1179, (30 June), 1967*
7. Adebahr, G., and Schewe, G.: Secondary lesions in brain injury in the area striata (Ger.) *Hefte Unfallheilk 94:261-263, 1968*
8. Adebahr, G., and Schewe, G.: Observation on the relation of primary and secondary injuries of the brain as a consequence of cranial pressure in relationship to time (Ger). *Deutsch Z Ges Gerichtl Med 59:118-124-1967*
9. Aebi, U.: Factors of increased risks of severe mental retardation (Ger). *Schweiz Med Wsch 98:47-54 (13 Jan), 1968*
10. Afra, D., and Nagy V.: The diagnostic significance of papilledema in closed craniocerebral injuries (Ger). *Zbl Neurochir 26:152-156, 1965*
11. Afra, D.: Neurosurgical procedures in injuries of the posterior cranial fossa (Ger). *Beitr Neurochir 8:148-151, 1964*
12. Agar, J. M.: Head injury in the adolescent: Medical complications in the early management. *Med J Aust 2:1182-1183, (17 Dec), 1966*
13. Aird, R. B., Venturini, A. M., and Spielman, P. M.: Antecedents of temporal lobe epilepsy. *Trans Amer Neurol Ass 91:10-13, 1966*
14. Akesson, H. O.: Condition at birth and mental deficiency. *Acta Genet (Basel) 16:283–304, 1966*
15. Anderson, H., and Gomes, S.: Craniosynostosis. Review of the literature and indications for surgery. *Acta Paediat Scand 57:47–54, (Jan), 1968*
16. Arnould, G., Lepoire, J., and Tridon, P.: Volitional postural syskinesias, sequelae of severe injuries of the brain stem in children (Apropos of 10 Cases) (Fre). *Rev Neurol (Paris) 114:150-157, (Feb), 1966*

17. Arseni, C., and Simionescu, M.: Growing skull fractures of childhood. A particular form of post-traumatic encephalopathy. *Acta Neurochir Wein) 15:159-172, 1966*

18. Aten, J., and Davis, J.: Disturbances in the perception of auditory sequence in children with minimal cerebral dysfunction. *J Speech Hearing Res 11:236-245, (June), 1968*

19. Auxter, D. M.: Proprioception among intellectually typical and differentially diagnosed educable mentally retarded boys. *Percept Motor Skills 21:751–756, (Dec), 1965*

20. Baker, D. H., and Berdon, W. E.: Special trauma problems in children. *Radiol Clin N Amer 4:289-305, (Aug), 1966*

21. Balestra, L., Mereto, G., and Amici, A.: Therapeutic possibilities of resuscitation of prolonged coma caused by cranial injury. (Ita). *Minerva Anest 32:485–495, (Sept), 1966*

22. Banerji, A. K., and Tandon, P. N.: Cranio-cerebral erosion and post-traumatic meningocele. *Neurol India 15:29–32, (Jan-Mar), 1967*

23. Barker, D. J.: Low intelligence. Its relation to length of gestation and rate of foetal growth. *Brit J Prev Soc Med 20:58-66, (April), 1966*

24. Barraquer, B. L.: On the clinical course of some extrapyramidal syndromes with onset in childhood. (Spa). *Prensa Med Argent 53:123–129, 1966*

25. Barrett, J. W., Mendelsohn, R. A.: Post-traumatic porencephaly in infancy. A report of three unusual cases. *J Neurosurg 23:522–527, (Nov), 1965*

26. Bartalena, G.: Grave hypoacusias of transmission due to cranial traumas without perceptive involvement, (Ita). *Boll Mal Orecch 83:460-469, (Jul-Aug), 1965*

27. Baumeister, A. A., and Kellas, G.: Memory for position in undifferentiated and brain-injured retardates and normals. *J Psychol 66:3-5, (May), 1967*

28. Bell, W. E.: The clinical approach to certain post-nataly acquired causes of mental retardation. *J Iowa Med Soc 55:60–64, (Feb), 1965*

29. Bemporad, J. R., Sours, J. A., and Spalter, H. F.: Cataracts following chronic headbanging: A report of two cases. *Amer J. Psychiat 125: 245–249, (Aug), 1968*

30. Benati, A., and Bricolo, A.: Post-traumatic rhinoliquorrhea (Ita). *Chir Ital 18:601–615, (Aug), 1966*

31. Bennek, J.: Cerebrospinal fluid chemistry in cranial traumas in childhood (Ger). *Zbl Chir 91:1878-1881, (10 Dec), 1966*

32. Bental, E., and Sharf, B.: Electroencephalographic changes following head injuries. *Electroenceph Clin Neurophysiol 24:192, (Feb), 1968*

33. Beraud, R., Bilodeau, B., and Sirois, J.: Traumatic thrombosis of the internal carotid artery (Fre). *Canad Med Ass J 94:537–541,* (12 *Mar*), *1966*

34. Bergamasco, B., Bergamini, L. and Doriguzzi, T.: Clinical value of the sleep electroencephalographic patterns in post-traumatic coma. *Acta Neurol Scand 44:495–511, 1968*

35. Bertoye, A., Freycon, F., and Humbert, G.: Late post-traumatic purulent meningitis. Apropos of 9 cases (Fre). *J Med Lyon 46:1993–2014, (5 Dec), 1965*

36. Bianchi, U. A., Samaja, B. A.: Intrauterine death of the fetus caused by maternal trauma. Considerations on 2 cases (Ita). *Minerva Ginec 19:238–244, (15 Mar), 1967*

37. Birch, H., Bortner, M.: Stimulus competition and concept utilization in brain damaged children. *Develop Med Child Neurol 9:402–410, (Aug), 1967*

38. Birch, H., Belmont, L., and Belmont, I.: Brain damage and intelligence in educable mentally subnormal children. *J Nerv Ment Dis 144: 247–257, (Apr), 1967*

39. Birch, H. G., and Walker, H. A.: Perceptual and perceptual-motor dissociation. Studies in schizophrenic and brain-damaged phychotic children. *Arch Gen Psychiat (Chicago) 14:113-118, (Feb), 1966*

40. Birrell, R. G., and Birrell, J. H.: The maltreatment syndrome in children: A hospital survey. *Med J Aust 2:1023–1029, (7 Dec), 1968*

41. Bizri, A.: Prevention of cerebral complications of the newborn caused by traumatism (Fre). *J Med Liban 18:269–274, (May–Jun), 1965*

42. Black, S. P., Ka , C. C., and Sights, W. P., Jr.s Aluminum cranioplasty. *Anesthesiology 29:562–564, (Nov–Dec), 1968*

43. Blumenfeld, S.: Some reflection on the problem of encephalopathies in childhood (ideas, framework, classification) (Fre). *Ann Medicopsychol (Paris) 2:715-724, (Dec), 1967*

44. Boenninghaus, H. G.: Recurrent meningitides as sequelae of earlier skull base fractures (Ger). *HNO 16:1-6, (Jan), 1968*

45. Boeters, U.: On the importance of initial amnesia in the evaluation of injury consequences. (Cerebral Traumatic Amnesia) (Ger). *Hefte Unfallheilk 94:250–256, 1968*

46. Bohm, E.: On the forensic assessment of cephalic hematoma (Ger). *Deutsch Z Ges Gerichtl Med 56:281-285, 1965*

47. Bolte, A., Steinmann, H. W., Beusch, C. H.: Childhood brain lesions after operative delivery. Catamestic and electroencephalographic studies after forceps delivery, vacuum extraction, breech, presentation and abdominal cesearean section (Ger). *Arch Gynaek 205:110-150, 1968*

48. Bottinelli, M. D., Mendilaharsu, C., Pereda, A.: Development of neuropsychic disorders in prolonged comas of traumatic origin (Spa). *Acta Neurol Lat Amer 11:137–150, 1965*

49. Bouzarth, W. F., Shenkin, H. A., and Feldman, W.: Adrenocortical response to craniocerebral trauma. *Surg Gynec Obstet 126:995–1001, (May), 1968*

50. Brandesky, G., Kotscher, E., Lorbek, W.: Skull fractures in children from the clinical and radiologic viewpoint. (Ger). *Radiol Austria 17:143–149, 1967*

51. Braun, F., and Jahna, H.: 102. Experience in the management of 367 severe covered head-brain injuries (HBI). (Ger). *Langenbeck Arch Klin Chir 319:604–619, 1967*

52. Bricolo, A.: Prolonged post-traumatic comas. Clinical and electroencephalographic study of 58 Cases. (Ita). *Minerva Neurochir 9:150–166, (Jul–Sept), 1965*

53. Bricolo, A., Gentilomo, A., Rosadini, G.: Long-lasting post-traumatic unconsciousness. A study based on nocturnal EEG and polygraphic recording. *Acta Neurol Scand 44:513-532, 1968*

54. Brown, O. L., Longacre, I. J., and Destefano, G. A.: Roentgen manifestations of blow-out fracture of the orbit. *Radiology 85:908-913, (Nov), 1965*

55. Browning, R. M.: Effect of irrelevant peripheral visual stimuli on discrimination learning in minimally brain-damaged children. *J Consult Psychol 31:371–376, (Aug), 1967*

56. Burton, C., Velasco, F., and Dorman, J.: Traumatic aneurysm of a peripheral cerebral artery. Review and case report. *J. Neurosurg 28: 468–474, (May), 1968*

57. Busch, E. A.: Brain stem contusions: Differential diagnosis, therapy, and prognosis. *Clin Neurosurg 9:18–33, 1963*

58. Cancura, W., and Gerstenbrand, F.: The vestibulo-ocular reflex as an aid in the diagnosis of acute brain stem lesions through constriction. (Ger). *Wien Z Nervenheilk 25:143–157, (Nov), 1967*

59. Carlsson, C. A., Von Essen, C., and Lofgren, J.: Factors affecting the clinical course of patients with severe head injuries. 1. Influence of biological factors. 2. Significance of post-traumatic coma. *J Neurosurg 29:242–251, (Sept), 1968*

60. Carrieri, G., and Anglani, D.: Transitory cerebral apoplexy in patients with cranial injuries with unusual internal carotid and vertebral anastomotic circulation. (Ita). *Osped Psichiat 34:361–374, (Jul–Dec), 1966*

61. Castelli, A., Paoletti, P., Villani, R.: Brain scan in cerebrovascular diseases and tumors. *Acta Neurochir (Wien) 17:217–227, 1967*

62. Charles J., Dalloz, J., and Meyer, B.: Cranial lacuna secondary to trauma in early infancy. (Fre). *Arch Franc Pediat 24:1029–1043, (Nov), 1967*

63. Chasler, C. N.: The newborn skull: The diagnosis of fracture. *Amer J Roentgen 100:92–99, (May), 1967*

64. Chevrie, J., and Aicardi, J.: Etiologic factors in flexion spasms of infants: Study of 81 cases (Fre). *Arch Franc Pediat 24:511-520, (May), 1967*

65. Choppy, M., Testard, C., and Zimbacca, N.: Psychological and clinical results of the action of a new cerebral stimulant studied in a neurosurgery department. (Fre). *Therapie 21:215–221, (Jan–Feb), 1966*

66. Churchill, J. A., Grisell, J., and Darnley, J. D.: Rhythmic activity in the EEG of newborns. *Electroenceph Clin Neurophysiol 21:131–139, (Aug), 1966*

67. Clark, K., Nash, T., *and* Hutchison, G.: The failure of circumferential craniotomy in acute traumatic cerebral swelling. *J Neurosurg 29: 367–371, (Oct), 1968*

68. Colman, P. G.: A comparative study of the test performances of brain-injured, emotionally disturbed and normal children. *S. Afr Med J 40:945-950, (22 Oct), 1966*

69. Columella, F., Gaist, G., Piazza, G.: On chronic cerebral laceration. Proposal of a new nosologic entity in cranial neurotraumatology. (Fre). *Neurochirurgie 14:703–716, (Jul-Aug), 1968*

70. Conners, C. K., and Barta, F., Jr.: Transfer of information from touch to vision in brain-injured and emotionally disturbed children. *J Nerv Ment Dis 145:138–141, (Aug), 1967*

71. Conners, C. K.: The syndrome of minimal brain dysfunction: Psychological aspects. *Pediat Clin N Amer 14:749-766, (Nov), 1967*

72. Connor, R. C.: Heart damage associated with intracranial lesions. *Brit Med J 3:29–31, (6 July), 1968*

73. Courville, C. B.: A pathological model for cerebral changes incident to paranatal anoxia. Report of a case of cerebral atrophy secondary to cardiorespiratory failure in infancy. *Amer J Dis Child 113:603–610, (May), 1967*

74. Crighel, E., and Solomonovici, A.: Electro-clinical correlations in closed cranio–cerebral injuries. *Electroenceph Clin Neurophysiol 22:572, (Jun), 1967*

75. Critchley, M.: Is developmental dylsexia the expression of minor cerebral damage. *Clin Proc Child Hosp DC 22:213–222, (Sept), 1966*

76. Crompton, M. R., Teare, R. D., and Bowern, D. A.: Prolonged coma after head injury. *Lancet 2:938–940, (29 Oct), 1966*

77. Crozzoli, N. R.: Statistical and therapeutic considerations on 517 patients with craniocerebral injuries. (Ita). *Minerva Med 57:745–753, (3 Mar), 1966*

78. Dalen, P.: Family history, the electroencephalogram and perinatal factors in manic conditions. *Acta Psychiat Scand 41:527–563, 1965*

79. Damanet, G.: The disruption of lateralized convulsions in childhood. (Fre). *Acta Neurol Belg 67:626–639, (Aug), 1967*

80. Dany, A., Boutet, P., and Gaudin, H.: Apropos of a case of post-traumatic acute subdural hematoma of the posterior fossa in a 17-month-old child. (Fre). *J Med Bordeaux 142:1997–2001, (Dec), 1965*

81. Dany, M. M., Boutet, P., and Gaudin, H.: Acute traumatic subdural hematoma of the posterior fossa in a 17-month-old infant. (Fre). *Neurochirurgie 12:539–541, (Sept-Oct), 1966*

82. Davis, J. H.: Medical examiner problems arising from neurosurgical cases. *Clin Neurosurg 12:300–311, 1964*

83. Delamonica, E. A.: Significance of electroencephalographic changes in cranio-cerebral trauma in children and adults. Considerations on their clinical, prognostic and mediocolegal value. (Spa.) *Prensa Med Argent 53:1372–1380, (24 Jun), 1966*

84. Derobert, L., Dehuve, A., Gillot, C.: Cerebral phlebography in craniocerebral injuries. Anatomic and radiologic aspects. (Fre). *Acta Med Leg Soc (Liege) 19:281-288, (Jul-Dec), 1966*

85. Deutsch, C. P., Zawel, D.: Comparison of visual and auditory perceptual functions of brain-injured and normal children. *Percept Motor Skills 22:303-309, (Feb), 1966*

86. Diemath, H. E.: The value of bitemporal relief surgery in severe closed skull brain trauma. (Ger). *Wien Med Wschr 116:1043-1044,* (26 *Nov*), *1966*

87. Dixon, C. C.: A look at sequential memory abilities of a group of ten brain-injured children. *Cereb Palsy J 28:6-8, (Sept-Oct), 1967*

88. Does, I. E., Bottema, T.: Post-traumatic conductive hearing loss. *Arch Otolaryng (Chicago) 82:331-339, (Oct), 1965*

89. Dohmen, M., and Kaufer, C.: Scalping injuries and their management. (Ger). *Chirurg 39:377-379, (Aug), 1968*

90. Dolce, G., Kaemmerer, E.: and Naquet, R.: On the significance of SW-complexes during photostimulation in patients with brain trauma. (Ger). *Nervenarzt 37:177-179, (Apr), 1966*

91. Drillien, C. M.: Studies in mental handicap. II. Some obstetric factors of possible aetiological significance. *Arch Dis Child 43:283-294, (Jun), 1968*

92. Dubo, H., Park D., and Pennington, R.: Serum-creatine-kinase in cases of stroke, head injury, and meningitis. *Lancet 2:743-748, (7 Oct), 1967*

93. Dunn, J., and Raskind, R.: Congenital skull fracture. *Calif Med 105:125-128, (Aug), 1966*

94. Editorial: Transient blindness and head injury in children. *Lancet 2: 820, (12 Oct), 1968*

95. Enge, S.: Electroencephalographic studies during the acute phase of recent closed skull-brain injuries. (Ger). *Wien Med Wschr 116:-417-422, (7 May), 1966*

96. Engel, K., Kutscha-Lissberg, E., and Maryhofer, O.: Studies of the comparibility of oxygen pressure and oxygen saturation in the blood of the severely ill. (Ger). *Anaesthesist 17:76-82, (Mar), 1968*

97. Ernhart, C. B., Graham, F. K., and Eichman, P. L.: Brain injury in the preschool child: Some developmental considerations. II. Comparison of brain injured and normal children. *Psychol Monogr 77:17-33, 1963*

98. Evans, J. P.: Recognition and management of late complications of head injuries. *Arizona Med 25:216-225, (Feb), 1968*

99. Fahy, T. J., Irving, M. H., and Millac ,P.: Severe head injuries. A six-year follow-up. *Lancet 2:475-479, (2 Sept), 1967*

100. Falsetti, H. L., and Moody, R. A.: Electrocardiographic changes in head injuries. *Dis Chest 49:420-424, (Apr), 1966*

101. Feore, D. R.: Blow-out fractures of the orbit. *Clin Radiol 16:347-350, (Oct), 1965*

102. Ferro-Milone, F., Pezzini, R., and Lorizio, A.: Clinical and electroencephalographic study of children who have suffered from perinatal hypoxia. (Ita). *Riv Neurobiol 13:11-39, (Jan-Mar), 1967*

103. Fleming, J. F., and Petrie, D.: Traumatic thrombosis of the internal carotid artery with delayed hemiplegia. *Canad J Surg 11:166-172, (Apr), 1968*

104. Fossati, P., Caridroit, M., and Pruvot, P.: Action of reserpine in posttraumatic comas in neurosurgery. Action on vigilance and precipitant role in neurogenic ulcer. (Fre). *Presse Med 73:2413-2418, (16 Oct), 1965*

105. Franke, K.: Incidence of skull-brain injuries in Berlin and problems of their management. (Ger). *Deutsch Gesundh 22:1982-1985, (19 Oct), 1967*

106. Freytag, E., and Lindenberg, R.: Neuropathologic findings in patients of a hospital for the mentally deficient. A survey of 359 cases. *Johns Hopkins Med J 121:379-392, (Dec), 1967*

107. Friedman, J., Strochak, R., and Gitlin, S.: Koppitz's Bender Scoring System and brain injury in children. *J Clin Psychol 23:179-182, (Apr), 1967*

108. Fritz, H.: Demonstration of a cerebrally radiation-injured child. (Ger). *Beitr Orthop Trauma 12:542-543, (Sept), 1965*

109. Froman, C.: Alterations of respiratory function in patients with severe head injuries. *Brit J Anaesth 40:354-360, (May), 1968*

110. Gallagher, J. P., and Browder, E. J.: Extradural hematoma. experience with 167 patients. *J Neurosurg 29:1-12, (Jul), 1968*

111. Galle, P., Staudacher, M.: Influence of diuretic drugs on the cerebrospinal fluid in cranial trauma. (Ger). *Med Klin 63:16-20, (5 Jan), 1968*

112. Garde, A., and Meunier, P.: Trial treatment of the subjective syndrome of head injuries with tegretol. (Fre), *Lyon Med 217:351-356, (29 Jan), 1967*

113. Gattini, E.: Contusion of the optic nerve in closed traumas of the head. (Ita). *Ann Ital Chir 42:173-177, 1965*

114. Gazzano, A. M., and Gorgerino, F.: The practical problems in resuscitation of patients with multiple injuries. (Ita). *Minerva Anest 32:497-503, (Sept), 1966*

115. Geisler, E., Viehweger, G., and Schippan, D.: Cerebrovascular processes in children. Contribution to cerebral thromboangiitis obliterans in childhood. (Ger). *Helv Paediat Acta 20:476-489, (Nov), 1965*

116. Gelehrter, G.: Skull fracture in the womb caused by a traffic accident. (Ger). *Mschr Unfallheilk 70:501-505, (Nov), 1967*

117. German, W. J., and Flanigan, S.: Examination and diagnosis in patients with head injury. *Clin Neurosurg 12:38-55, 1964*

118. Gilbert, M. M.: Post-concussion syndrome: Its etiology and treatment by inhalation of carbon dioxide and oxygen. *Southern Med J. 59: 1155-1160, (Oct), 1966*

119. Gilbert, R. G., and Brindle, G. F.: Head injuries. *Int Anesth Clin 4:881-895, (Winter), 1966*

120. Gisela and Goldhahn, W. E.: Leading symptom: Cerebrospinal fluid discharge from the nose. (Ger). *Chirurg 38:126-131, (Mar), 1967*

121. Glatthaar, E., and Weber, M.: On early and late damage in children following vacuum extraction. (Ger). *Gynaecologia (Basel) 162:335-340, 1966*

122. Glowinski, M., Norska, I., and Krysowska, A.: The intra partum cerebral trauma in full term infants in the light of clinical experiences. (Ger). *Zbl Gynaek 89:1275-1281, (2 Sept), 1967*

123. Gomez, J. C., Asenjo, A., and Fierro, G. J.: Diagnostic errors in encephalocranial trauma. (Spa). *Neurocirugia 24:133-142, (Jul-Dec), 1966*

124. Griffith, J. F., and Dodge, P. R.: Transient blindness following head injury in children. *New Eng J Med 278:648-651, (21 Mar), 1968*

125. Grote, W.: Traumatic frontobasal cerebrospinal fluid fistulae. (Ger). *Chirurg 37:102-105, (Mar), 1966*

126. Gruber, L., and Steer, M.: Perception expression and intelligence in institutionalized mentally retarded children. *Amer J Ment Defic 71:417-422, (Nov), 1966*

127. Gurdjian, E. S., Thomas, L. M., and Hodgson, V. R.: Impact head injury. *GP 37:78-87, (Feb), 1968*

128. Hagan, P. J.: Posttraumatic anosmia. *Arch Otolaryng (Chicago) 85:85-89, (Jan), 1967*

129. Hall, G. M., and Hallberg, O. E.: Persistent cerebrospinal fluid otorrhea. *Arch Otolaryng (Chicago) 86:377-381, (Oct), 1967*

130. Hamblen, D. L.: Occipito-cervical fusion. Indications, technique and results. *J Bone Joint Surg (Brit) 49:33-45, (Feb), 1967*

131. Harrison, A.: Specificity of neonatal anoxia in the EEG pattern of the child of school age who shows praxic or speech difficulties. (Fre). *Rev Neurol (Paris) 117:101-105, (Jul), 1967*

132. Haupt, H.: Early signs, symptomless intermediary stages and late lesions after fetal hypoxia. (Ger). *Mschr Kinderheilk 115:215-216, (Apr), 1967*

133. Hawkes, C. D.: Craniocerebral trauma in infancy and childhood. *Clin Neurosurg 11:66-75, 1964*

134. Hawtof, D. B.: Intracranial hemorrhage in burned patients, reports of four cases. *J Trauma 6:503-506, (Jul), 1966*

135. Hendrick, E. B., Harwood-Hash, D. C., and Hudson, A. R.: Head injuries in children: A survey of 4465 consecutive cases at the hospital for sick children, Toronto, Canada. *Clin Neurosurg 11:46-65, 1964*

136. Hendry, W. T., and Stalker, A. L.: Stab wound of medulla by handle of metal comb. *Med Sci Law 7:213-215, (Oct), 1967*

137. Hirschenfang, S., Silber, M., and Benton, J. G.: Psychological appraisal of the brain injured. *J Rehab 33:23-24, (Sept-Oct), 1967*

138. Hitschler, W. J.: Facial palsy of unusual etiology. *Laryngoscope 76:549-554, (Mar), 1966*

139. Hochleitner, M.: Circumscribed post-traumatic scleroderma as a convulsant disease. (Ger). *Wien Klin Wschr 78:460-463, (24 Jun), 1966*

140. Hollin, S. A., Sukoff, M. H., and Silverstein, A.: Post-traumatic middle cerebral artery occlusion. *J Neurosurg 25:526-535, (Nov), 1966*

141. Holroyd, J.: Cross validation of the Quast and Koppitz's Bender-Gestalt signs of cerebral dysfunction. *J. Clin Psychol 22:200, (Apr), 1966*

142. Holroyd, J.: When WISC verbal IQ is low. *J Clin Psychol 24: Suppl: 457, (Oct), 1968*

143. Hooper, R.: Head injury in the adolescent: Neurosurgical considerations. *Med J Aust 2:1184-1185, (17 Dec), 1966*

144. Horvath, L.: Aetiology of mental deficiency. *Acta Morph Acad Sci Hung Suppl 13:29-38, 1965*

145. Hossack, D. W., and King, A.: Neurogenic heterotropic ossification. *Med J Aust 1:326-328, (18 Feb), 1967*

146. Hough, J.V., and Stuart, W.D.: Middle ear injuries in skull trauma. *Laryngoscope 78:899-937, (Jun), 1968*

147. Howell, T. R.: Accidents and those bizarre bicycles. *Pediatrics 42:214, (Jul), 1968*

148. Hudson, H., and Von Bennewitz, A.: Severe encephalocranial injury in children. Statistical evaluation of elementary diagnostic principles. (Spa). *Neurocirugia 23:82-87, (Jan-Dec), 1965*

149. Hunter, A.: Perinatal events and permanent neurological sequelae. *New Zeal Med J 68:108-113, (Aug), 1968*

150. Hutt, C.: Exploration of novelty in children with and without upper CNS lesions and some effects of auditory and visual incentives. *Acta Psychol (Amst) 28:150-160, (Apr), 1968*

151. Hutt, C., Hutt, S. J., and Ounsted, C.: The behavior of children with and without upper CNS lesions. *Behaviour 24:246-268, 1965*

152. Illingworth, G., and Jennett, W. B.: The shocked head injury. *Lancet 2:511-514, (11 Sept), 1965*

153. Isfort, A.: Bilateral traumatic subdural hematoma in a small child with hemophilia. (Ger). *Zbl Neurochir 28:155-159, 1967*

154. Ito, H., Kudo, Y., and Kabeshima, Y.: Double-blind controlled trial of Lucidril (Meclofenoxate) in the post-traumatic syndrome, especially dizziness. *Folia Psychiat Neurol Jap 22:23-42, 1968*

155. Jackson, F. E., Hart, G., and Bonneson, C.: "Hidden" intracranial hematomas: Their diagnosis and treatment. *Milit Med 132:888-892, (Nov), 1967*

156. Jacobs, L., and Jacobs, J.: Hypnotizability of children as related to hemispheric reference and neurological organization. *Amer J Clin Hypn 8:269-274, (Apr), 1966*

157. Jakab, I.: The role of neonatal anoxia and its prevention. *Acta Paedopsychiat (Basel) 32:329-338, (Nov), 1965*

158. Jellinger, K.: Frequency and pathogenesis of central brain lesions after blunt injury of the skull. (Ger). *Wien Z Nervenheilk 25:223-249, (Nov), 1967*

159. Jensen, H. P.: 97. Head-brain injuries in childhood. (Ger). *Langenbeck Arch Klin Chir 319:590-594, 1967*

160. Jones, W. R.: Fractured pelvis in pregnancy with severe foetal skull injury. *J Obstet Gynaec Brit Comm 73:491-493, (Jun), 1966*

161. Jonsson, C. O., Lidvall, H., and Malhammar, G.: An exploratory psychological study of the post-traumatic cerebral syndrome. *Acta Neurol Scand 43:158-166, 1967*

162. Kahn, E. A.: The clinical applications of brain scanning. *Clin Neurosurg 12:23-37, 1964*

163. Kaltschev, J., and Tschomakov, M.: Wounds at the point of bullet entrance in long distance gunshot injuries. (Ger). *Deutsch Z Ges Gerichtl Med 61:48-52, 1967*

164. Kalyanaraman, S., and Ramamurthi, B.: Extradural haemorrhage. A review of 17 cases. *J. Indian Med Ass 50:199-201, (1 Mar), 1968*

165. Karimi-Nejad, A., and Krenkel, W.: Gas gangrene-brain abscess following a "scalp wound". (Ger). *Deutsch Med Wschr 91:1231-1233, (8 Jul), 1966*

166. Kazner, E., and Schiefer, W.: Echoencephalographic findings in craniocerebral injuries. (Ger). *Acta Radiol (Diagn) (Stockholm) 5:832-842, 1966*

167. Kendall, B. S.: Orientation errors in the Memory-For-Designs Test: Tentative findings and recommendations. *Percept Motor Skills 22: 335-345, (Apr), 1966*

168. Khedroo, L. G.: Craniocerebral injuries: The application of generalized surface body cooling (hypothermia). *Int Surg* 47:554-564, *(Jun), 1967*

169. Kinal, M. E.: Traumatic thrombosis of dural venous sinuses in closed head injuries. *J. Neurosurg 27:142-145, (Aug), 1967*

170. Kirsch, A. P.: Diagnosis of cerebrospinal fluid rhinorrhea: Lack of Specificity of the glucose oxidase test tape. *J. Pediat 71:718-719, (Nov), 1967*

171. Klar, S., and Piotrowski, W.: On the problems of expanding skull fractures. (Ger). *Langenbeck Arch Klin Chir 316:381-384, 1966*

172. Kline, D. G.: Atlanto-axial dislocation simulating a head injury: Hypoplasia of the odontoid. (Case report.) *J. Neurosurg 24:1013-1016, (Jun), 1966*

173. Klonoff, H. Robinson, G. C.: Epidemiology of head injuries in children: A pilot study. *Canad Med Ass J 96:1308-1311, (13 May), 1967*

174. Kloss, L., and Bosmuller, H.: Open and closed frontal bone fractures with and without impression and their treatment. (Ger). *Klin Med (Wien) 22:441-445, 1967*

175. Klug, W.: Accident-induced, perforating cranio-cerebral injuries with orbital involvement. (Ger). *Zbl Neurochir 29:45-53, 1968*

176. Knights, R. M., Hyman, J. A., and Wozny, M. A.: Psychomotor abilities of familial, brain-injured and mongoloid retarded children. *Amer J Ment Defic 70:454-457, (Nov), 1965*

177. Knobloch, H., and Pasamanick, B.: Prediction from the assessment of neuromotor and intellectual status in infancy. *Proc Amer Psychopath Ass 56:387-400, 1967*

178. Koch, H.: Follow-up examination following severe skull injuries possibly with base fractures that had not been surgically treated (150 cases) (Ger). *Z Aerztl Fortbild* (Jena) *60:239-241, (1 Mar), 1966*

179. Kondo, S., Hamano, K., and Sakai, A.: Statistical studies on the brain injuries, their occurrence, treatment, and prognosis. *Bull Osaka Med Sch 12:48-58, (Apr), 1966*

180. Kong, E.: Early diagnosis and early treatment of cerebral movement disorders ("paralyses"), with demonstration of treatment results. (Ger). *Praxis 54:1280-1284, (4 Nov), 1965*

181. Krauel, U.: Intracerebral traumatic hematoma. (Ger). *Schweiz Arch Neurol Neurochir Psychiat 98:197-239, 1966*

182. Krenkel, W.: "Acute skull-brain injury"—Misleading anamneses. (Ger). *Hefte Unfallheilk 94:256-260, 1968*

183. Kriens, O., and Pfeifer, G.: On growth disorders following injuries of the mid-face bones in the 1st years of life. (Ger). *Fortschr Kiefer Gesichtschir 12:106-116, 1967*

184. Kruse, R.: Unusual EEG findings following cerebral trauma due to lightning in a child. A case of latent epilepsy. (Ger). *Deutsch Z Nervenheilk 188:53-61, (12 Jan), 1966*

185. Kubala, M. J., and Kellaway, P.: Cerebral concussion in children—A longitudinal EEG profile. *Electroenceph Clin Neurophysiol 23:82, (Jul), 1967*

186. Kugler, J., and Rieger, H.: Dependency of trauma sequelae on various pre-existing conditions. (Ger). *Wien Med Wschr 117:120-123, (4 Feb), 1967*

187. Kuhlo, W.: The 4-5/Sec EEG basic rhythm variant in sleep and following contusio cerebri. (Ger). *Arch Psychiat Nervenkr 210:68-75, (8 Aug), 1967*

188. Kumpmann, U.: On the use of a proteolytic enzyme in traumatology and general surgery. (Ger). *Bruns Beitr Klin Chir 211:93-103, (Aug), 1965*

189. Kurze, T., and Pitts, F. W.: Management of closed head injuries. *Surg Clin N Amer 48:1271-1278, (Dec), 1968*

190. Lambooy, N., Van Der, Zwan, A., and Fossen, A.: End-results after long-term unconsciousness due to head-injury. *Psychiat Neurol Neurochir 68:431-442, (Nov-Dec), 1965*

191. Landis, M. S.: Cerebral angiography for the family physician and community hospital. *J Amer Osteopath Ass 66:44-57, (Sept), 1966*

192. Lausberg, G.: Cranial gunshot injuries in peace time. (Ger). *Acta Neurochir (Wien) 13:517-543, 1965*

193. Lecuire, J. Goutelle, A., and Spay, G.: Therapeutic indications in traumatic thromboses of the internal carotid artery (Apropos of 10 Cases). (Fre). *Neurochirurgie 11:295-302, (Jul-Aug), 1965*

194. Lecuire, J. Lapras, C., and Goutelle, A.: Extradural prefrontal hematomas: Apropos of 18 cases. (Fre). *Neurochirurgie 13:431-443, (May June), 1967*

195. Lehman, R. A. Hayes, G. J., and Martins, A. N.: The use of adhesive and lyophilized dura in the treatment of cerebrospinal rhinorrhea. Technical Note. *J Neurosurg 26:92-95, (Jan), 1967*

196. Le Moine, M. and Beeckmans-Balle, M.: Importance of complications in the perinatal period in scholastic maladjustment. (Fre). *Acta Paediat Belg 21:389-406, 1967*

197. Lenard, H. G.: EEG changes in recent skull injuries in childhood. (Ger). *Munchen Med Wschr 107:1820-1827, (17 Sept), 1965*

198. Lepoire, J. Cordier, J., and Laxenaire, M.: Apropos of 2 nonfatal cases transfixing wounds of the brain stem. (Fre). *Rev Otoneuroophtal 38:176-185, (Jul-Aug), 1966*

199. Lewis, G. M. and Brice, J.: Traumatic posterior fossa extradural haematoma. *Proc Roy Soc Med 60:246, (Mar), 1967*

200. Lie, T. S.: Skull-brain injury and EEG in childhood. (Ger). *Zbl Chir 92:2458-2466, (2 Sept), 1967*

201. Lindgren, S. O.: Experimental studies of mechanical effects in head injury. *Acta Chir Scand 360:Suppl 360:1+, 1966*

202. Liss, L., and Mervis, L.: Spontaneous ventriculostomy through lamina terminalis with arrest of hydrocephalus. A case report. *J Neurosurg 23:211-213, (Aug), 1965*

203. Little, W. J.: On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities. *Clin Orthop 46:7-22, (May-Jun), 1966*

204. Lloyd, G. A.: Orbital emphysema. *Brit J Radiol 39:933-938, (Dec), 1966*

205. London, P. S.: Some observations on the course of events after severe injury of the head. Hunterian Lecture delivered at the Royal College of Surgeons of England on 12th January, 1967. *Ann Roy Coll Surg Eng 41:460-479, (Dec), 1967*

206. Longacre, J. J., Kahl, J. B. and Wood, R. W.: Reconstruction of extensive defects in and about the orbit. *Amer J Ophthal 61:763-768, (Apr), 1966*

207. Low, M. B.: Accidents and those bizarre bicycles. *Pediatrics 42:214, (Jul), 1968*

208. Luzzatto, A., and Ghiotto, A.: Changes in glutamic-oxalacetic and glutamic-pyruvic transaminases in injured patients. (Ita). *Chir Ital 18:616-632, (Aug), 1966*

209. Lyle, D. J.: Ophthalmological appraisal of cerebral impairment in infants and children. (Stressing natal and post-natal trauma). *Trans Ophthal Soc Uk 85:275-287, 1965*

210. McAninch, M.: Who is this child they call "brain-injured". *Cereb Palsy J 26:13-15, (Jul-Aug), 1965*

211. McConnell, O. L.: Koppitz's Bender-Gestalt Scores in relation to organic and emotional problems in children. *J Clin Psychol 23:370-374, (Jul), 1967*

212. McLaurin, R. L., and Helmer, F.: The syndrome of temporal-lobe contusion. *J Neurosurg 23:296-304, (Sept), 1965*

213. Mansell, P. W., and Hunt, A. C.: Major head injuries in fights and brawls. *Med Sci Law 8:181-187, (Jul), 1968*

214. Massa, T., and Niedermeyer, E.: Convulsive disorders during the first three months of life. *Epilepsia (Amst) 9:1-19, (Mar), 1968*

215. Mastrogiovanni, P. D.: On a case of bilateral paralysis of the abducens nerve of traumatic origin. (Ita). *Rass Neuropsichiat 19:717-726, (Oct-Dec), 1965*

216. Matsuoka, K., Sakaki, S., and Okamoto, E.: A clinico-pathological study on the causes of hemorrhagic lesions in the brain stem with head injury. *Med J Osaka Univ 17:257-266, (Mar), 1967*

217. Matzker, J.: Binaural click test after blunt skull injuries. (Ger). *Z Laryng Rhinol Otol 47:159-167, (Mar), 1968*

218. Mealey, J., Jr., and Campbell, J. A.: Scintillography of infantile subdural effusions and its clinical application. *Acta Radiol (Diagn) (Stockholm) 5:871-883, 1966*

219. Meloche, B. R., Sansregret, A., and Gregoire, H.: A case of post-traumatic leptomeningeal cyst. (Fre). *Un Med Canada 96:1214-1219, (Oct), 1967*

220. Messerklinger, W.: On the microscopic, intraoperative function examination of nasal and paranasal sinus mucosa as an aid for the localization of minute cerebrospinal fluid fistulae. (Ger). *Mschr Ohrenheilk 101:355-371, 1967*

221. Metzger, J., Proteau, J., and Sayac, G.: Posttraumatic rhinorrhea. (Fre). *Ann Med Leg (Paris) 45:423-438, (Sept-Oct), 1965*

222. Meurice, E.: Signs of diurnal falling asleep in a group of post-concussion patients compared with a group of normal subjects. (Fre). *Rev Neurol (Paris) 115:524-526, (Sept.), 1966*

223. Meyer, H. J.: Chiasmal trauma. (Ger). *Klin Mbl Augenheilk 146:833-848, (Aug), 1965*

224. Meyer, J. S., Gotoh, F., Ebihara, S.: Effects of anoxia on cerebral metabolism and electrolytes in man. *Neurology (Minneap) 15:892-901, (Oct) 1965*

225. Meyer, J. S., Gotoh, F., and Favale, E.: Effects of carotid compression on cerebral metabolism and electroencephalogram. *Electroenceph Clin Neurophysiol 19:362-376, (Oct), 1965*

226. Miller, H.: Medicolegal aspects of head injury. *Curr Med Drugs 7:3-9, (Apr), 1967*

227. Miller, J. D., and Ayers, T. N.: Post-traumatic changes in the internal carotid artery and its branches: An arteriographic study. *Radiology 89:95-100, (Jul), 1967*

228. Miller, J. D., and Jennett, W. B.: Complications of depressed skull fracture. *Lancet 2:991-995, (9 Nov), 1968*

229. Mincy, J. E.: Posttraumatic cerebrospinal fluid fistula of the frontal fossa. *J Trauma, 6:618-622, (Sept), 1966*

230. Mises, J., and Lerique, A.: The lennox syndrome following trauma. *Electroenceph Clin Neurophysiol 24:489-490, (May), 1968*

231. Mondini P. and Manfredi L.: On a very serious case of cranial splitting with vast pneumocephalus treated with cranioplasty. (Ita.) *Boll Soc Medicochir Cremona 19:205-214, (Jan-Dec), 1965*

232. Monod, N.: Ways of estimation of neonatal anoxia and electroencephalographic studies. (Fre). *Rev Neurol (Paris) 117:99-100, (Jul), 1967*

233. Moor, S.: Unusual erosive defects in the skull following trauma in children. *New Zeal Med J 68:94-98, (Aug) 1968*

234. Morel-Maroger, A., Philippon, J., and Bories, J.: Traumatic arteriovenous aneurysms of the middle menigeal artery. (Fre) *Rev Neurol (Paris) 116:428-429, (May), 1967*

235. Morello, G., Sanna, G., and Turchiaro, G.: Clinico-statistical considerations on post-traumatic epilepsy. (Ita). *Rass Neuropsichiat 19:617-632, (Jul-Sept), 1966*

236. Morin, A.: Determination of body damage during the abatement of fractures of the anterior floor of the base of the cranium. (Fre). *Lyon Med 220:231-252, (11 Aug), 1968*

237. Mounier-Kuhn, P., Morgan, A., and Achache, R.: Apropos of 200 vestibulograms performed with "oscillating" electronystamography in head-injury patients. (Fre). *Rev Otoneuroophtal 39:246-251, (Jul-Aug), 1967*

238. Muller, E.: On trauma of the aging and preexisting vascular damage of the brain. (Ger). *Deutsch Z Nervenheilk 188:259-270, (8Mar), 1966*

239. Muller, E. and Neymann, R.; Repeated craniocerebral trauma. (Ger). *Mschr Unfallheilk 70:422-432, (Oct), 1967*

240. Muller, H.: Piercing injuries and foreign bodies in the retrostyloid space (Ger). *HNO 14:314-316 (Oct), 1966*

241. Muller, H. R.: Diagnosis of Epidural hematoma in the preclinical stage, on the value of routine echoencephalography in skull vault fractures. (Ger). *Schweiz Med Wschr 97:1055-1057, (12 Aug), 1967*

242. Muss, I.: The rehabilitation of a patient with brain stem injury, *Southern Med J 59:1046-1050, (Sept), 1966*

243. Naquet, R., Vigouroux, R., and Choux, M.: Electroencephalographic study of recent cranial injuries in a resuscitation department. (Fre). *Rev Neurol (Paris) 117:512-513, (Sept), 1967*

244. Nathan, F.: Some considerations on fulminating cerebral concussion. (Ita). *Minerva Medicoleg 85:110-116, (May-Jun), 1965*

245. Niswander, K. R., Turoff, B. B. and Romans J.: Development status of children delivered through elective induction of labor, Results of a 4-year follow-up study. *Obstet Gynec 27:15-20, (Jan), 1966*

246. Nivoli, G.C.: Clinical observations on the use of a benzodiazepinic derivative in post-traumatic states of mental and motor excitation (Ita). *Minerva Med 59:5051-5056, (Nov), 1968*

247. Noordenbos, W.: Traumatic carotid–cavernous fistula. *Psychiat Neurol Neurochir 71:93–98, (Jan–Feb), 1968*

248. Noterman, J.: States of shock and cranial injury (Fre). *Acta Chir Belg 66:451–452, (May), 1967*

249. Nunes, A.: Embolism, aspiration and deglutition of brain tissue. (Fre). *Ann Med Leg (Paris) 46:329–333, (Sep–Oct), 1966*

250. Obes Polleri, J.: Trial of glycerin in cerebral injury in the newborn. (Spa). *Arch Pediat Urug 36:603–604, (Sep), 1965*

251. Oeken, F. W.: Clinical contribution to carotid arrosion hemorrhage. (Ger). *HNO 13:311–314, (Nov), 1965*

252. Oganesjan, S. S.; Intracranial cysts and dystrophic bone defects in closed cerebrocranial trauma in childhood. (Ger). *Beitr Neurochir 8:124–127, 1964*

253. Ojemann, R. G., Weber, A. L., and Smith, A.: Cranial trauma. Use of large bifrontal decompression in the treatment of severe head injuries in children. *Clin Pediat (Phila) 5:165–170, (Mar) 1966*

254. O'Leary, J. L.: Electroencephalography in head trauma. *Clin Neurosurg 12:171–180, 1964*

255. Olivier, L., Strauss, M. F. and David, M.: Positive and negative aspects of Echo-Encephalography, remarks on cranial injuries (Fre). *Presse Med 75:2213–2216, (25 Oct), 1967*

256. Orsini, A., Louchet, E., and Vigouroux, R.: Considerations on 3 cases of endocranial suppuration. (Fre). *Arch Franc Pediat 24:113–114, (Jan), 1967*

257. Ozer, M. N.: Symposium: The Role of Sensory Experience in the Maturation of Sensorimotor Function in Early Infancy. 3. Clinical Applications. *Clin Proc Child Hosp (Wash) 22:279–282, (Oct), 1966*

258. Paal, G.: Accidents and brain tumor from clinical diagnostic viewpoint. (Ger). *Med Welt 5:295–299, (3 Feb), 1968*

259. Paillas, J. E., Pellet, W., and Demard, F.: Osteomenigeal fistulas of the base of the skull with leakage of cerebrospinal fluid. (Study of 102 Cases). (Fre). *J Chir (Paris) 94:295–316, (Oct), 1967*

260. Paine, R. S.: Prenatal and perinatal factors affecting the central nervous system. *Clin Proc Child Hosp DC 24:277–293, (Sept), 1968*

261. Palm, D.: On the diagnosis and judgment of the course of subdural effusions in infants and preschool children. I. Clinical, and encephalographic studies. (Ger). *Z Kinderheilk 98:16–33, 1967*

262. Palm, D.: On the diagnosis and judgment of course of subdural effusions in infancy and preschool age. II. Electronencephalographic studies. (Ger). *Z Kinderheilk 98:34–50, 1967*

263. Passouant, P., Cadilhac, J., and Pternitis, C.: Temporal epilepsy and ammon's horn discharges induced by oxygen deficiency anoxia. (Fre). *Rev Neurol (Paris) 117:65-70, (Jul), 1967*

264. Paul, J.: The abuse of brain damaged children. (Ger). *Mschr Kinderheilk 115:202–206, (Apr), 1967*

265. Payne, E. E.: Unusual fatal brain injury due to knitting-needle. *Brit Med J 2:807-808, (Oct), 1966*

266. Pertuiset, B., More–Maroger, A., and Philippon, J.: Traumatic arteriovenous aneurysms of the middle meningeal artery. (Fre). *Presse Med 75:2775–2778, (25 Dec), 1967*

267. Petz, R., and Meyer, J.: Some problems of concurrent traumatic injuries in the midfacial region (Ger). *Deutsch Stomat 18:720-733, (Oct), 1968*

268. Pia, H. W.: Cerebral injuries in children and their acute complications. (Ger). *Munchen Med Wschr 108:760–768, (Apr), 1966*

269. Pignataro, O., and Albano, V.: Statistical considerations on cupulometric tests in cranial injuries (Fre). *Pract Otorhinolaryng (Basel) 28: 405-411, 1966*

270. Pincini, G., Perani, G., and Piati, A.: Cochleovestibular sequelae of injuries of the face and frontal area. (Ita). *Arch Ital Otol 77:98–105, (Jan–Feb), 1966*

271. Pitner, S. E.: Carotid thrombosis due to intraoral trauma. An unusual complication of a common childhood accident. *New Eng J Med 274:764–767, (7 Apr), 1966*

272. Plueckhahn, V. D.: Head injury in the adolescent: Pathological factors complicating its early management. *Med J Aust 2:1185–1189, (17 Dec), 1966*

273. Pond, D.: Communication disorders in brain-damaged children. *Proc Roy Soc Med 60:343-348, (Apr) 1967*

274. Pothe, H.: On diagnosis and therapy of epidural hemorrhage. (Ger). *Deutsch Med Wschr 91:1186–1192, (1 Jul), 1966*

275. Potter, J. M.: Head injury and haemophilia *Acta Neurochir (Wien) 13:380–387, 1965*

276. Prechtl, H. F.: Neurological sequelae of prenatal and perinatal complications. *Brit Med J 4:763–767, (30 Dec), 1967*

277. Rao, B. D., Reddy, M. V., and Subrahmanian, M. V.: The physiological basis of unconsciousness and aphasia in acute head injuries. *Neurol India 15:15–19, (Jan–Mar), 1967*

278. Rao, B. D., Subrahmanian, M. V., and Reddy, M. V.: Mortality in acute head injuries. *Neurol India 15:1–5, (Jan–Mar) 1967*

279. Raskind, R.: Surgical repair of a leptomeningeal cyst due to trauma: Case report. *Int Surg 47:411-415, (May), 1967*

280. Raskind, R., and Doria, A.: Cerebrospinal fluid rhinorrhea and otorrhea of traumatic origin. *Int Surg 46:223-227, (Sept), 1966*

281. Ravenna, C., and Benedetti, A.: Pre- and Post-Operative EEG Observations in 12 patients undergoing total hemispherectomy. (Ita.) *Riv Pat Nerv Ment 86:155-169, (Apr), 1965*

282. Ravenna, C., and Semerano, A.: The evolution of primary epileptogenic foci in childhood (Clinical and electroencephalographic correlations). (Ita). *Riv Pat Nerv Ment 87:466–480, (Oct), 1966*

283. Ravenna, C., Andrioli, G., and Mingrino, S.: Electroencephalographic changes in the course of prolonged registration in patients in post-traumatic coma. (Ita). *Riv Neurol 38:95–99, (Mar), 1968*

284. Ravenna, C., Denes, F., and Rigon, D.: Late clinical and electroencephalographic aspects of children delivered with forceps. (Ita). *Riv Neurol 38:95-99, (Mar-Apr), 1968*

285. Ravenna, C., and Lion, P.: Observations on 2 cases of post-traumatic status epilepticus. (Ita). *Riv Neurol 37:19–28, (Jan–Feb), 1967*

286. Raynor, R., and Parsa, M.: Nonsurgical elevation of depressed skull fracture in an infant. *J Pediat 72:262–264, (Feb), 1968*

287. Reeves, D. L.: Penetrating craniocerebral injuries. Report of two unusual cases. *J Neurosurg 23:204–205, (Aug), 1965*

288. Regel, H., Parnitzke, K. H., and Fischel, W.: The application of graphical methods in diagnosing early cerebral lesions. (Ger). *Acta Paedopsychiat (Basel) 32:338–343 Concl, (Nov), 1965*

289. Regel, H., Parnitzke, K. H., and Fischel, W.: The application of graphical methods in the diagnosis of early infantile brain lesions. (Ger). *Acta Paedopsychiat (Basel) 32:299-307 Contd, (Oct), 1965*

290. Reichelt, A., and Schweikert, C. H.: Fracture healing in cranioceberal injuries (Ger). *Heffte Unfallheilk 91:250-252, 1967*

291. Reid, W. B., Moore, D., and Alexander, D.: Abbreviated form of the WISC for use with brain-damaged and mentally retarded children. *J Consult Clin Psychol 32:236, (Apr), 1968*

292. Reilly, H. P., Jr., Erbengi, A., and Sachs, E., Jr. Penetration of the sagittal sinus by a pressed skull fracture, roentgenographic diagnosis in an asymptomatic boy. JAMA 202:841–842, (20 Nov), 1967

293. Rennick, P. M., and Halstead, W. C.: Color-naming, delayed speech feedback and cerebral dysfunction. *J Clin Psychol 24:155–161, (Apr), 1968*

294. Rodin, E. A.: Contribution of the EEG to prognosis after head injury. *Dis Nerv Syst 28:595–601, (Sept), 1967*

295. Rosen, M. G., and Satran, R.: The neonatal electroencephalogram. Clinical applications. *Amer J Dis Child 111:133–141, (Feb), 1966*

296. Rosenblith, J. F.: Judgments of simple geometric figures by children. *Percept Motor Skills 21:947–990, (Dec), 1965*

297. Rosner, S.: Surgical pathology and treatment of complicated cerebral palsy. *Angiology 17:77–84, (Feb), 1966*

298. Schaaf, L., Waldschock, E. and Fahlisch, K.: Report on the late results of surgically treated fresh cerebrocranial injuries in an accident clinic. (Ger). *Chirurg 39:53–56, (Feb), 1968*

299. Schain, R. J.: Minimal brain dysfunction in children: A neurological viewpoint. *Bull Los Angeles Neurol Soc 33:145–155, (Jul), 1968*

300. Schecter, M. M., Zingesser, L. H., and Rayport, M.: Torn meningeal vessels: An evaluation of a clinical spectrum through the use of angiography. *Radiology 86:686-695, (Apr), 1966*

301. Scherzer, E.: The normal echoencephalogram and its significance in traumatology. (Ger). *Wien Klin Wschr 78:301–304, (29 Apr), 1966*

302. Schiebel, A.: Our results in the treatment of open skull injuries. (Ger). *Chirurg 37:171–174, (Apr), 1966*

303. Schiefer, W., Lewke, M., and Kazner, E.: Hemorrhagic shock as the leading symptom for the recognition of post-traumatic intracranial hematomas in infancy and early childhood. (Ger). *Zbl Neurochir 29:131–138, 1968*

304. Schneider, R., and Boles, R.: Combined neuro-otologic and neurosurgical problems in head trauma. *Laryngoscope 78:955–972, (Jun), 1968*

305. Schneider, P.: Loss of vision in closed skull injuries. (Fre). *Ophthalmologica (Basel) 156:377–384, 1968*

306. Schneider, D., Kubicki, S., and Haeusler, H.: Follow-up studies of children having undergone blood microanalysis during birth. (Ger). *Gynaecologia (Basel) 164:174–190, 1967*

307. Schnuriger, V.: Electroencephalographic findings in the organic psychical syndromes of children and adolescents. (Ger). *Acta Paedopsychiat (Basel) 33:118–144, (Apr–May), 1966*

308. Schubert, W., and Eisenkratzer, F.: On an easily avoidable source of accidents in childhood. (Ger). *Deutsch Gesundh 23:636–638, (4 Apr), 1968*

309. Schulte, F. J., Filipp, E., and Michaelis, R.: Neurology of the newborn. II. Prognosis of functional disturbances of the central nervous system in the newborn. (Ger). *Z Kinderheilk 93:264–276, (23 Aug), 1965*

310. Schulte, F., Michaelis, R., and Filipp, E.: Neurology of the newborn. I. Causes and clinical symptomatology of functional disorders of the nervous system of the newborn. (Ger). *Z Kinderheilk 93:242–263, (23 Aug), 1965*

311. Schurmann, K., Dietz, H., Fischer, F.: Problems of parenteral nutrition in neurosurgery. (Ger). *Zbl Neurochir 28:209–216, 1967*

312. Schwandt, R., Riemer, C.: Contribution to head contusion with a fatal outcome in childhood. (Ger). *Mschr Unfallheilk 69:442–446, (Sept), 1966*

313. Schyra, B., and Krumbholz, S.: Findings and complications in the treatment of skull fractures with brain injuries. (Ger). *Mschr Unfallheilk 69:587–595, (Dec), 1966*

314. Secondi, U., and Nazari, G.: Glutamic oxalacetic and glutamic pyruvic transaminase activity of the cerebrospinal fluid in cranial injuries and various otovestibular diseases. (Ita). *Riv Otoneurooftal 41:197–212, (May–Jun), 1966*

315. Secondi, U., and Nazari, G.: On the pathogenesis of some traumatic cerebral vascular diseases. (Ita). *Riv Anat Pat Oncol 28:712–740, (Nov–Dec), 1965*

316. Seeger, W.: Frontobasal fractures. (Ger). *Deutsch Med Wschr 92:1009–1012, (2 Jun), 1967*

317. Selecki, B.R., Hoy, R.J., and Ness, P.; A retrospective survey of neurotraumatic admissions to a teaching hospital. 1. General aspects. *Med J Aust 2:113–117, (15 Jul), 1967*

318. Selecki, B., Hoy, R., and Ness, P.; Neurotraumatic admissions to a teaching hospital: A retrospective study: 4. Neurotrauma after road accidents. *Med J Aust 2:490–493, (21 Sept), 1968*

319. Selecki, B., Hoy, R., and Ness, P.: Neurotraumatic admissions to a teaching hospital: A retrospective survey. 2. head injuries. *Med J Aust 1:582–585, (6 Apr), 1968*

320. Seligmann, F.: Neurologic and electroencephalographic sequelae in 52 cases of cranial injuries in children, and therapeutic indications. (Fre). *Rev Neuropsychiat Infant 13:439–451, (Jun–Jul), 1965*

321. Seligmann, F.: The affective sequelae of cranial injuries and their possible relation to EEG alterations. (Fre). *Rev Neuropsychiat Infant 13:517–529, (Jun–Jul), 1965*

322. Shimizu, S., Oda, Y., and Handa, H.: A statistical survey of traffic accidents, especially of head injuries in and outside Kyoto in 1966, together with a comparison with data for 1961. *Arch Jap Chir* 36; *862–873, (1 Nov), 1967*

323. Simonsen, J.: Fatal subarachnoid haemorrhage in relation to minor head injuries. *J Forensic Med 14:146–155, (Oct–Dec). 1967*

324. Skurczynski, W.: Air rifle gunshot wounds in the region of the neck and head. (Ger). *HNO 13:223–226, (Aug), 1965*

325. Smith, J. L.: Some neuro-ophthalmological aspects of head trauma. *Clin Neurosurg 12:181–192, 1964*

326. Spence, W. T.: Head injuries "then and now" or diagnosis and treatment of head injuries 1939 versus 1965. *Med Ann DC 36:102–104, (Feb), 1967*

327. Spirito, L., and Braito, A.: Asphyxic syndromes in the course of whooping cough. (Ita). *G Mal Infett 18:426–430, (Jun), 1966*

328. Staats, O. J., Ceballos, R., and Miller, R. E.: Brain tissue embolization secondary to cerebral trauma. *Alabama J Med Sci 2:394–396, (Oct), 1965*

329. Steinbereithner, K., and Wagner, O.: Studies on the behavior of acid-base equilibrium and respiratory gases in cerebrospinal fluid and arterial blood in severe skull injuries with special reference to the hyperventilation syndrome. (Ger). *Klin Wschr 45:126–133, (1 Feb), 1967*

330. Steinmann, H. W.: Clinical, pathological-anatomical and electroencephalographic correlation in the acute posttraumatic phase. (Ger). *Beitr Neurochir 14:101–108, 1967*

331. Steps, H. J.: On osmotherapy with urea and sorbitol in the ENT specialty. (Ger). *HNO 14:68–69, (Mar), 1966*

332. Stockert, F. G. Von: The problem of vulnerability. (Ger). *Acta Paedopsychiat (Basel) 33:101–109, (Apr–May), 1966*

333. Stowell, A., and Kauth, J. E.: The value of echo-encephalography in acute and chronic head injuries. *J Okla Med Ass 60:494–496, (Sept), 1967*

334. Stowsand, D., and Geile, G.: Cerebral symptoms in impression fractures of the skull convexity. (Ger). *Deutsch Z Nervenheilk 189:330–344, (24 Oct), 1966*

335. Stowsand, D.: Concerning the healing of bone clefts after impression-fracture of the skull convexity. (Ger). *Arch Psychiat Nervenkr 208: 472–481, 1966*

336. Tallian, F., Puskas, E., and Hernady, A.: On the effect of breech presentation of the fetus. (Results of Follow-Up Studies). (Ger). *Acta Chir Acad Sci Hung 6:375–383, 1965*

337. Tenti, L., and Borghi, A.: Cerebral angiographic data in patients with recent cranial injuries. (Case Reports). (Ita). *Minerva Radiol 11:97–116 (Mar), 1966*

338. Testa, C., and Nizzoli, V.: Long-term prognosis in infantile evolutive cranial fractures. Neuropsychological changes and medicolegal considerations. (Ita). *Minerva Medicoleg 86:325–329, (Nov–Dec), 1966*

339. Testa, C., and Nizzoli, V.: Growing fractures in closed cranial injuries in early childhood resulting in the composition of a cranial lacuna. (Fre). *Neurochirurgie 14:111–134, (Mar), 1968*

340. Thunold, S., and Ro, J.: Embolism of cerebellar tissue to the pulmonary arteries following head injury. *Acta Path Microbiol Scand 64:485–490, 1965*

341. Till, K.: Subdural haematoma and effusion in infancy. *Brit Med J 2:400–402, (17 Aug), 1968*

342. Todd, E. M., Crue, B. L., Jr.: Depressed fractures of the skull in infants. Surgical management. *Amer J Surg 113:479–481, (Apr), 1967*

343. Troupp, H.: Intraventricular pressure in patients with severe brain injuries. II. *J Trauma 7:875–883, (Nov), 1967*

344. Ueki, K.: Hemispherectomy in the human with special reference to the preservation of function. *Progr Brain Res 21:285–338, 1966*

345. Unger, R. R., and Siedschlag, W. D.: Echoencephalography and closed cerebrocranial injuries. (Ger). *Mschr Unfallheilk 69:435–442, (Sept), 1966*

346. Valladares, H., Matus, A., and Varleta, J.: Water-salt balance in cerebrocranial trauma. (Spa). *Neurocirugia 24:148–152, (July–Dec), 1966*

347. Valladares, H., Matus, A., and Varleta, J.: Electrolytes in cerebrocranial trauma. Clinical and laboratory study. I. Biochemical study of the internal environment. (Spa). *Neurocirugia 24:153–161, (Jul–Dec), 1966*

348. Vas, C. J., and Winn, J. M.: Growing skull fractures. *Develop Med Child Neurol 8:735–740, (Dec), 1966*

349. Vedel-Jensen, N.: Pathological ocular fixation instability. (Photonystagmographic investigations of ocular fixation movements in patients suffering from the post-traumatic cerebral syndrome, and disseminated sclerois, compared to normal subjects. *Acta Ophthal (Kobenhavn) 44:481–493, 1966*

350. Vedrinne J., and Spay, G.: Thrombosis of the Internal carotid and its branches after closed trauma. Medico-legal considerations apropos of 13 cases. (Fre). *Ann Med Leg (Paris) 47:154–174, (Mar–Apr), 1967*

351. Vensi, E.: Functional results of deafness due to head injury: Statistical considerations on audiometric damage. (Ita). *G Veneto Sci Med 20:57–67, (Mar–Apr), 1965*

352. Wagemann, W., and Ahlborn, J.: Studies on late development of deafness following skull injuries (Ger). *HNO 13:256–264, (Sept), 1965*

353. Wallner, H., and Rosefeldt, H.: A contribution on intrauterine skull fracture and on trauma related intrauterine fetal death. (Ger). *Geburtsh Frauenheilk 26:980–985, (Jun), 1966*

354. Warrington, E. K., James, M., and Kinsbourne, M.: Drawing disability in relation to laterality of cerebral lesion. *Brain 89:53–82, (Mar), 1966*

355. Watts, C. C., Clark, K., and McConnell, T. H.: Fetal head trauma without maternal uterine injury. *Amer J Obstet Gynec 99:289–290, (15 Sept), 1967*

356. Weinstein, E. A.: Conversion hysteria after brain injury. *Trans Amer Neurol Ass 91:361–362, 1966*

357. Weinstein, E. A., and Lyerly, O. G.: Confabulation following brain injury. Its analogues and sequelae. *Arch Gen Psychiat (Chicago) 18:348–354, (Mar), 1968*

358. Weinstein, E. A., and Lyerly, O. G.: Conversion hysteria following brain injury. *Arch Neurol (Chicago) 15:545–548, (Nov), 1966*

359. **Wenzel, K. P.**: On the value of urea therapy in closed cerebrocranial traumas (Ger). *Zbl Chir 90:2146–2150, (9 Oct), 1965*

360. **Werner, M. A.**, and **Berney, J.**: Skiing and craniocerebral injuries. (Fre). *Neurochirurgie 13:774–780, (Nov), 1967*

361. **Whitacre, W. B.**: Dislocation of the mandibular condyle into the middle cranial fossa: Review of the literature and report of a case. *Plast Reconstr Surg 38:23–26, (Jul), 1966*

362. **White, R. J.**, **Verdura, J.**, and **Locke, G. E.**: Emergency cerebral arteriography in acute head injury. *Angiology 17:72-76, (Feb), 1966*

363. **Whittlesey, W.**, and **McAfee, R. O.**: Behavior problems of the minimally brain-injured child. *J Okla Med Ass 60:395-401, (Jul), 1967*

364. **Widrow, S. A.**: The diagnosis of minimal brain damage. *J Med Soc New Jersey 63:47-50, (Feb), 1966*

365. **Wieczorek, V.**, and **Greger, J.**: Experiences with cerebrospinal fluid cell diagnosis, an analysis of about 5000 cytological examinations. II. cell picture in inflammatory brain and spinal cord diseases, after brain damage in early childhood, in degenerative diseases of the central nervous system, epilepsy and endogenous psychoses. (Ger). *Psychiat Neurol (Basel) 150:104-117, 1965*

366. **Windle, W. F.**: Asphyxia at birth, a major factor in mental retardation: Suggestions for prevention based on experiments in monkeys. *Proc Amer Psychopath Ass 56:140-147, 1967*

367. **Windle, W. F.**: Brain damage at birth. Functional and structural modifications with time. *JAMA 206:1967-1972, (Nov), 1968*

368. **Wise, J. H.**: Performance of neurologically impaired children copying geometric designs with sticks. *Percept Motor Skills 26:763-772, (Jun), 1968*

369. **Work, H. H.**, and **Haldane, J. E.**: Cerebral dysfunction in children. A review, *Amer J Dis Child 111:573-580, (June), 1966*

370. **Wowern, F. Von**: Obesity as a sequel of traumatic injury to the hypothalamus. *Danish Med Bull 13:11-13, (Mar), 1966*

371. **Wright, J .W., Jr.**, and **Taylor, C. E.**: Advantages of tomography in trauma. *Laryngoscope 78:973-985, (Jun), 1968*

372. **Wright, R. L.**: Traumatic hematomas of the posterior cranial fossa. *J Neurosurg 25:402-409, (Oct), 1966*

373. **Yashon, D.**, **Jane, J. A.**, **White, R. J.**: Arteriographic observations in craniocerebral bullet wounds. *J. Trauma 8:238-255, (Mar), 1968*

374. **Yoshii, N.**, **Moriyama, M.**, and **Iisaki, Y.**: Electroencephalographic survey of the head injuries: 333 clinical cases. *Keio J Med 14:123-133, (Sept), 1965*

375. **Zander, E.**, **Foroglou, G.**, and **Oberson, R.**: Surgical indications in internal post-traumatic hydrocephalus. (Fre). *Neurochirurgie 14:13-26, (Jan-Feb), 1968*

376. **Zanibelli, G.**, and **Boriani, A.**: Some considerations on the value of the otoneurologic examination in cranial-injured patients. (Clinical Contribution). (Ita) *Boll Soc Medicochir Cremona 18:835-847, (Oct-Dec), 1964*

377. **Zucker, J. M., Chodkiewicz, J. P., and Sultan, Y.**: Traumatic intracerebral hematoma, successfully operated in a hemophiliac. (Fre). *Nouv Rev Franc Hemat 8:406-408, (May-Jun), 1968*

378. **Zwirner, R.**: The social background in the postconcussion syndrome. (Ger). *Hefte Unfallheilk 91:246-250, 1967*

☆U.S. GOVERNMENT PRINTING OFFICE: 1970 O—379-244